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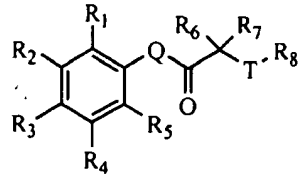
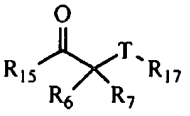
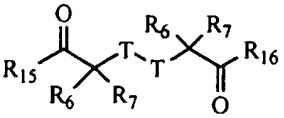
(54) Title: CARBONYL COMPOUNDS AS INHIBITORS OF HISTONE DEACETYLASE FOR THE TREATMENT OF DISEASE

(I) 

(II) 

(III) 

(57) Abstract: Disclosed herein are carbonyl compounds of Formula (I), (II) or (III), and others as described herein. Also disclosed are methods of treating disease, such as cancer, neurological disorders, including polyglutamine-repeat disorders, anemias, thalassemias, inflammatory conditions, autoimmune diseases and cardiovascular conditions, using the compounds of the invention. In addition, methods of modulating the activity of histone deacetylase (HDAC) are also disclosed.

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CARBONYL COMPOUNDS AS INHIBITORS OF HISTONE DEACETYLASE FOR THE TREATMENT OF DISEASE

CROSS REFERENCE TO RELATED APPLICATION

This Application claims priority of U.S. provisional application Serial No. 60/477,721, filed June 10, 2003.

FIELD OF THE INVENTION

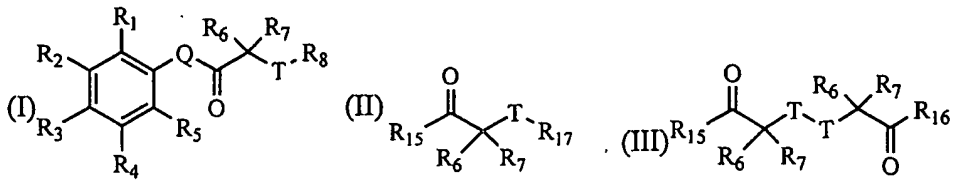
[0001] The present invention is directed to carbonyl compounds as inhibitors of histone deacetylase (HDAC). These compounds are useful in treatments of disease states, including, but not limited to, certain cancers (such as colon cancer, breast cancer, ovarian cancer, lung cancer, prostate cancer, cancers of the pancreas, cervix, uteri, kidney, brain and central nervous system, non-Hodgkin's lymphoma, multiple myeloma and hematopoietic malignancies including leukemias (Chronic Lymphocytic Leukemia) and lymphomas), neurological disorders, including polyglutamine-repeat disorders (such as Huntington's disease, Spinocerebellar ataxia 1 (SCA 1), Machado-Joseph disease (MJD)/Spinocerebella ataxia 3 (SCA 3), Kennedy disease/Spinal and bulbar muscular atrophy (SBMA) and Dentatorubral pallidolusyian atrophy (DRPLA), anemias and thalassemia (such as Sickle Cell Disease (SCD), inflammatory conditions (such as Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD), ulcerative colitis and psoriasis) autoimmune diseases (such as Systemic Lupus Erythromatosus (SLE) and Multiple Sclerosis (MS)) and cardiac hypertrophy and heart failure.

BACKGROUND OF THE INVENTION

[0002] Histone proteins organize DNA into nucleosomes, which are regular repeating structures of chromatin. The acetylation status of histones alters chromatin structure, which, in turn, is involved in gene expression. Two classes of enzymes can affect the acetylation of histones - histone acetyltransferases (HATs) and histone deacetylases (HDACs). A number of HDAC inhibitors have been characterized. However, to date no effective candidate for cancer therapy has been identified. Therefore, there is a need in the art to discover HDAC inhibitors that have effective anti-tumor activity.

SUMMARY OF THE INVENTION

[0003] Disclosed herein are carbonyl compounds of Formula I, II, or III and related Formulae IV, V, VI VII, or VIII, as described herein, including their pharmaceutically acceptable salts, esters, and prodrugs.

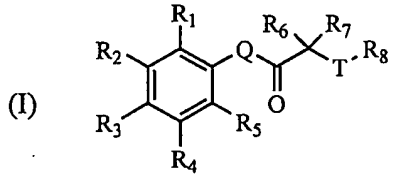


[0004] Also disclosed are pharmaceutical compositions comprising a compound having structural formulae I, II, III, IV, V, VI, VII or VIII which are capable of inhibiting the catalytic activity of histone deacetylase (HDAC).

[0005] Also disclosed are methods of treating diseases in mammals, including humans, such as cancer, using the compounds of the invention. In addition, methods of modulating the activity of histone deacetylase (HDAC) are also disclosed.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0006] An aspect of the present invention relates to a compound of Formula I



or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,

wherein

a) R_1-R_5 is each independently selected from the group consisting of

i) hydrogen;

ii) lower alkyl;

iii) lower alkylene;

iv) halogen or perhaloalkyl;

v) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2, or 3; and

vi) a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2, or 3

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

G) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl, aryl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

H) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, heteroalkyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, heteroalkyl, aryl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

vii) an acyl of formula $-(X_1)_{n1}-C(O)-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, aryl, heteroaryl, hydroxy, alkoxy, amino, and $-NH-X_3$,

where X_3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, amino, and amide; and

n1 is 0, 1, 2, or 3; and

viii) cyano;

ix) nitro;

x) an amino of formula $-(X_{15})_{n15}-NX_{16}X_{17}$, where

X_{15} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_{16} and X_{17}, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n15 is 0 or 1;

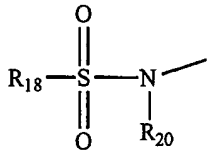
xi) thioether or thiol of formula $-(X_{22})_{n22}-S-X_{23}$, where

X_{22} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{23} is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl, aryl, and heteroaryl; and

n22 is 0, 1, 2, or 3;

xii) an N-sulfonamido of structure



wherein

R_{18} is a lower alkyl, lower heteroalkyl, or is a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, perhalolkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2, or 3;

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the

nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0, or 1;

G) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, aryl, heteroaryl, and perfluoroalkyl; and

n6 is 0, 1, 2, or 3; and

H) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

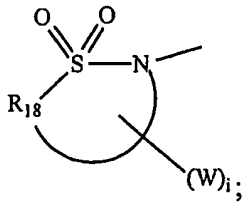
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, heteroaryl, heteroalkyl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, and heteroaryl, and heteroalkyl;

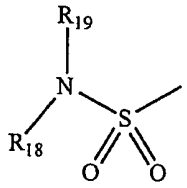
n7 and n9 are each independently is 0 or 1;

R_{20} is H, lower alkyl, lower aralkyl, or R_{20} taken together with R_{18} forms an optionally substituted five-, six-, seven-, or eight-membered heterocyclic ring, as shown below:



and wherein i is 0, 1, 2, 3, 4;

xiii) an S-sulfonamido of formula



wherein R_{18} is lower alkyl, lower heteroalkyl, or a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2 or 3:

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

G) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, aryl, perfluoroalkyl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

H) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

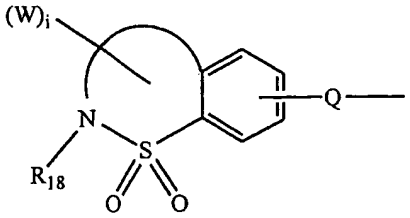
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

R_{19} is H, C_{1-5} alkyl, C_{1-5} aralkyl, or taken together with one of R_1, R_2, R_3, R_4, or R_5, said R_{19} forms an optionally substituted five-, six-, seven-, or eight-membered heterocyclic ring, as shown below:



i is 0, 1, 2, 3, 4;

or R_1 and R_2, taken together along with the two ring carbons to which they are attached, or R_2 and R_3, taken together along with the two ring carbons to which they are attached, or R_3 and R_4, taken together along with the two ring carbons to which they are attached, or R_4 and R_5, taken together along with the two ring carbons to which they are attached, form a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a six-membered aromatic or heteroaromatic, or a five- or six-membered heteroaromatic ring, each of which is optionally substituted with one or more substituents, W, each of which is independently selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) optionally substituted aryl;

iv) optionally substituted heterocyclyl;

v) an alkoxy of formula $-(X_{13})_{n13}-O-X_{14}$, where

X_{13} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{14} is selected from the group consisting of hydrogen, lower alkyl, aryl, perhaloalkyl, and heteroaryl; and

n13 is 0, 1, 2, or 3;

vi) halogen or perhaloalkyl;

vii) cyano;

viii) nitro;

ix) an amino of formula $-(X_{15})_{n15}-NX_{16}X_{17}$, where

X_{15} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_{16} and X_{17}, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n15 is 0 or 1; and

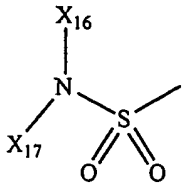
x) a thioether or thiol of formula $-(X_{22})_{n22}-S-X_{23}$, where

X_{22} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{23} is selected from the group consisting of hydrogen, lower alkyl, perfluoroalkyl, aryl, and heteroaryl; and

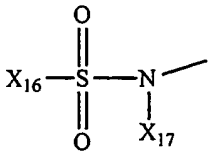
n22 is 0, 1, 2, or 3;

xxii) an S-sulfonamido of formula



wherein X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, lower heteroalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

xxiii) an N-sulfonamido of structure



wherein X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, lower heteroalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

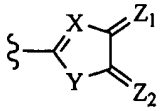
b) R_6 and R_7 are each independently selected from the group consisting of hydrogen and lower alkyl;

c) R_8 is selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) cyano;

iv) 

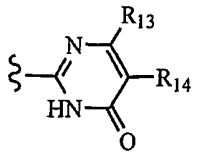
wherein

X is selected from CH and nitrogen;

Y is selected from the group consisting of CH_2, NH, oxygen and sulfur;

Z_1 and Z_2 are each independently selected from the group consisting of null, oxygen, sulfur, and $CR_{11}R_{12}$,

wherein R_{11} and R_{12} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy; and

v) 

wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy;

vi) optionally substituted acyl, $-C(O)R_E$, wherein $HOC(O)R_E$ is any pharmaceutically acceptable acid;

vii) or R_8 is equivalent to the balance of Formula I to form a disulfide dimer;

d) Q is selected from the group consisting of a bond, oxygen, sulfur, $-(CH_2)_m-$, $-(CH_2)_m NH-$, $-(CH_2)_m (CO)-$, $-(CH_2)_m NH(CO)-$, and $-(CH_2)_m C(O)NH-$, wherein m is 0-7, wherein if Q is not symmetric, Q may be attached in either direction; and

e) T is selected from the group consisting of oxygen, sulfur, and $-NR_{17}$, wherein R_{17} is selected from the group consisting of hydrogen, lower alkyl, and aryl.

[0007] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound of the invention with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound of the invention with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[0008] The terms "physiologically acceptable" and "physiologically compatible" refers to excipients, products, or hydrolysis products of disclosed molecular embodiments of the invention. By way of example, protected thiol prodrug embodiments may release acids upon hydrolysis of the protected thiol. Physiologically acceptable excipients and acids are those that do not abrogate the biological activity or properties of the compound, and are nontoxic. "Physiologically acceptable" and "pharmaceutically acceptable" may be coextensive terms.

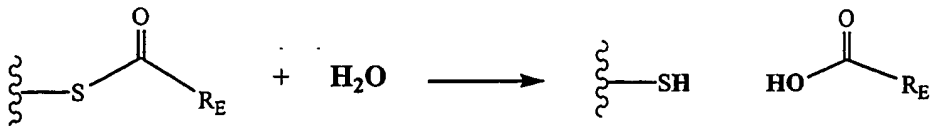
[0009] The term "ester" refers to a chemical moiety with formula -$(R)_n$-COOR', where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1.

[0010] An "amide" is a chemical moiety with formula -$(R)_n$-C(O)NHR' or -$(R)_n$-NHC(O)R', where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1. An amide may be an amino acid or a peptide molecule attached to a molecule of the present invention, thereby forming a prodrug.

[0011] Any amine, hydroxy, or carboxyl side chain on the compounds of the present invention can be esterified or amidified. The procedures and specific groups to be used to achieve this end is known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein in its entirety.

[0012] The term "lower perfluoroalkoxy" refers to a radical –O-$(CX_2)_nCX_3$ where X is any halogen, preferable F or Cl, and n is 1-5.

[0013] A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. Yet another example of a prodrug are protected thiol compounds. Thiols bearing hydrolyzable protecting groups can unmask protected SH groups prior to or simultaneous to use.



[0014] The term thiol protecting group refers to thiols bearing hydrolyzable protecting groups that can unmask protected SH groups prior to or simultaneous to use. Preferred thiol protecting groups include but are not limited to thiol esters which release pharmaceutically acceptable acids along with an active thiol moiety. Such pharmaceutically acceptable acids are generally nontoxic and do not abbrogate the biological activity of the active thiol moiety. Examples of pharmaceutically acceptable acids include, but are not limited to:

N,N-diethylglycine;
4-ethylpiperazinoacetic acid;
ethyl 2-methoxy-2-phenylacetic acid;
N,N-dimethylglycine;
(nitrophenoxysulfonyl)benzoic acid;
Acetic acid;
Maleic acid;
Fumaric acid;
Benzoic acid;
Tartraric acid;
Natural amino acids (like glutamate, aspartate, cyclic aminoacids such praline);
D-amino acids;
Butyric acid;
Fatty acids like palmitic acid, stearic acid, oleate;
Pipecolic acid;
Phosphonic acid;
Phosphoric acid;
pivalate (trimethylacetic acid);
Succinic acid;
Cinnamic acid;
Anthranilic acid;
Salicylic acid;
Lactic acid; and
Pyruvic acids.

[0015] The term "aromatic" refers to an aromatic group which has at least one ring having a conjugated pi electron system and includes both carbocyclic aryl (e.g., phenyl)

and heterocyclic aryl groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups. The term "carbocyclic" refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon. The term "heteroaromatic" or "heteroaryl" refers to an aromatic group which contains at least one heterocyclic ring.

[0016] A carbocyclic or heterocyclic ring may be aliphatic. In this case, the ring is either completely saturated, or if there is unsaturation, the conjugation of the pi-electrons in the ring do not give rise to aromaticity. The term "heterocyclyl" thus refers to a heterocyclic aliphatic or a heterocyclic aromatic (i.e., a heteroaryl) ring. Likewise, the term "carbocyclyl" refers to a carbocyclic aliphatic or a carbocyclic aromatic (i.e., an aryl) ring.

[0017] As used herein, the term "alkyl" refers to an aliphatic hydrocarbon group. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[0018] The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group of the compounds of the invention may be designated as "C_1-C_5 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl.

[0019] The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto,

alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. Wherever a substituent is described as being "optionally substituted" that substitutent may be substituted with one of the above substituents.

[0020] The substituent "R" appearing by itself and without a number designation refers to a substituent selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl (bonded through a ring carbon) and optionally substituted heteroalicyclic (bonded through a ring carbon).

[0021] An "O-carboxy" group refers to a RC(=O)O- group, where R is as defined herein.

[0022] A "C-carboxy" group refers to a –C(=O)OR groups where R is as defined herein.

[0023] An "acyl" group refers to a –C(=O)R group.

[0024] An "acetyl" group refers to a $-C(=O)CH_3$, group.

[0025] A "trihalomethanesulfonyl" group refers to a $X_3CS(=O)_2$- group where X is a halogen.

[0026] A "cyano" group refers to a –CN group.

[0027] An "isocyanato" group refers to a –NCO group.

[0028] A "thiocyanato" group refers to a –CNS group.

[0029] An "isothiocyanato" group refers to a –NCS group.

[0030] A "sulfinyl" group refers to a –S(=O)-R group, with R as defined herein.

[0031] A "S-sulfonamido" group refers to a $-S(=O)_2NR$, group, with R as defined herein.

[0032] A "N-sulfonamido" group refers to a $RS(=O)_2NH$- group with R as defined herein.

[0033] A "trihalomethanesulfonamido" group refers to a $X_3CS(=O)_2NR$- group with X and R as defined herein.

[0034] An "O-carbamyl" group refers to a –OC(=O)-NR, group-with R as defined herein.

[0035] An "N-carbamyl" group refers to a ROC(=O)NH- group, with R as defined herein.

[0036] An "O-thiocarbamyl" group refers to a –OC(=S)-NR, group with R as defined herein.

[0037] An "N-thiocarbamyl" group refers to an ROC(=S)NH- group, with R as defined herein.

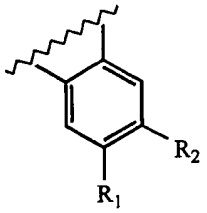
[0038] A "C-amido" group refers to a –C(=O)-NR_2 group with R as defined herein.

[0039] An "N-amido" group refers to a RC(=O)NH- group, with R as defined herein.

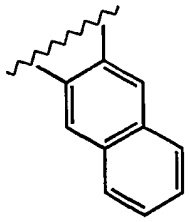
[0040] The term partially halogenated alkyl refers to an alkyl group having both hydrogen and halogen substituents.

[0041] The term "perhaloalkyl" refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0042] When two substituents taken together along with the two ring carbons to which they are attached form a ring, it is meant that the following structure:



is, for example, representative of a structure such as the following:



[0043] In the above example, R_1 and R_2, taken together along with the two ring carbons to which they are attached, form a six-membered aromatic ring.

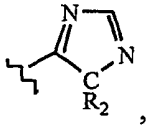
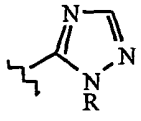
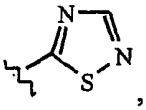
[0044] Unless otherwise indicated, when a substituent is deemed to be "optionally substituted," it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from cycloalkyl, aryl, heteroaryl,

heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

[0045] In certain embodiments, the invention relates to a compound of Formula I where R_1-R_5 are hydrogen.

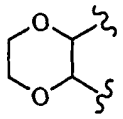
[0046] In other embodiments R_2 is an alkoxy. The alkoxy may be selected from the group consisting of methoxy, ethoxy, propoxy, n-butoxy, t-butoxy, and isobutoxy. In some embodiments, R_3 is an alkoxy.

[0047] In certain embodiments, R_3 is a halogen. "Halogen" refers to a substituent selected from the group consisting of fluorine, chlorine, bromine, and iodine. Thus, in some embodiments the halogen may be chlorine, whereas in other embodiments, the halogen may be bromine. In still other embodiments, R_3 is a perhaloalkyl. The perhaloalkyl may be selected from the group consisting of trifluoromethyl, pentafluoroethyl, and heptafluoropropyl.

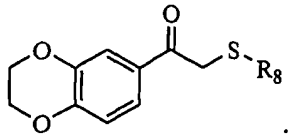
[0048] In some embodiments, R_3 is a heterocyclyl. The heterocyclyl may be selected from the group consisting of furan, thiophene, pyrrole, pyrroline, pyrrolidine, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, triazole, thiadiazole, pyran, pyridine, piperidine, morpholine, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine,  ,  , and  , where R is as defined herein. In some embodiments the heterocyclyl is pyrrolidine, whereas in other embodiments, the heterocyclyl is morpholine.

[0049] In certain embodiments, R_3 is –NH(CO)R, where R is as defined herein. In some embodiments, R is selected from hydrogen, and lower alkyl, where the alkyl may be selected from the group consisting of methyl, ethyl, propyl, n-butyl, t-butyl, and isobutyl.

[0050] In some embodiments, R_2 and R_3, taken together along with the two ring carbons to which they are attached form a six-membered heterocyclic ring. In certain of these embodiments, the six-membered heterocyclic ring has the following structure:

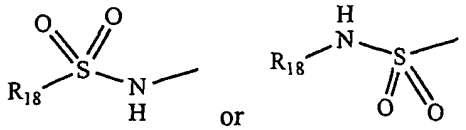


Thus, in some embodiments, the compound of Formula I will have the following structure:



[0051] In some embodiments R_3 or R_4 is an optionally substituted N-sulfonamido or an optionally substituted S-sulfonamido.

[0052] In some embodiments R_3 or R_4 has the structure



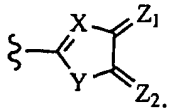
or

wherein R_{18} is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl.

[0053] In some embodiments R_{18} is phenyl, singly or multiply substituted with C_{1-5} alkyl, C_{1-5} perhaloalkyl, C_{1-5} alkoxy, C_{1-5} perhaloalkyl alkoxy, and N-alkylamido..

[0054] In some embodiments R_6 and R_7 are hydrogen.

[0055] In certain embodiments, R_8 is cyano. In other embodiments, R_8 is

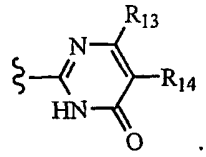


[0056] In some of these embodiments, X is nitrogen, Y is oxygen and Z_1 and Z_2 are H_2, whereas in other embodiments, X is nitrogen, Y is NH, Z_1 is oxygen and Z_2 is H_2. In still other embodiments, X is nitrogen, Y is NH, and Z_1 and Z_2 are oxygen, while in other embodiments, X is nitrogen, Y is sulfur, Z_1 is (H)(OH) and Z_2 is H_2.

[0057] When Z_1 or Z_2 are H_2, it is meant that the ring carbon to which Z_1 or Z_2 are attached forms a methylene (-CH_2-)group. When Z_1 or Z_2 are oxygen, it is meant that the ring carbon to which Z_1 or Z_2 are attached forms a carbonyl (-C(O)-) group. When Z_1 or Z_2

are (H)(OH), it is meant that the ring carbon to which Z_1 or Z_2 are attached forms a hydroxymethylene (-CH(OH)-) group.

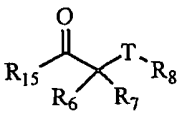
[0058] In certain other embodiments, R_8 is

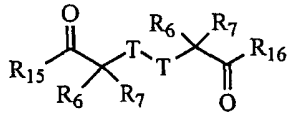


[0059] In some of these embodiments, R_{13} and R_{14} are hydrogen, whereas in other embodiments, R_{13} is lower alkyl and R_{14} are hydrogen, where the alkyl may be selected from the group consisting of methyl, ethyl, propyl, n-butyl, t-butyl, and isobutyl.

[0060] In certain embodiments, the present invention relates to a compound of Formula I where T is sulfur. In other embodiments, T is oxygen, whereas in yet other embodiments, T is –NR.

[0061] In another aspect, the present invention relates to a compound of Formula II or III,

(II) 

(III) 

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,

or a pharmaceutical composition comprising such compounds,

wherein

a) T is selected from the group consisting of oxygen, sulfur, and $-NR_{17}$, wherein R_{17} is selected from the group consisting of hydrogen, lower alkyl, and aryl;

b) R_{15} and R_{16} are each independently selected from the group consisting of

i) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2, or 3; and

ii) a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2 or 3

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

G) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

H) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

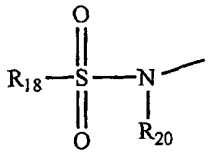
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

I) an N-sulfonamido of structure



wherein

R_{18} is a lower alkyl, lower heteroalkyl, or five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

(1) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

(2) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2 or 3;

(3) halogen or perhaloalkyl;

(4) cyano;

(5) nitro;

(6) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

(7) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, perfluoroalkyl, aryl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

(8) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

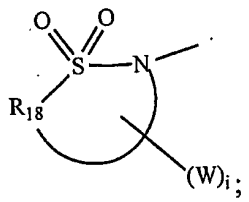
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, lower heteroalkyl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, lower heteroalkyl, and heteroaryl;

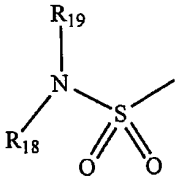
n7 and n9 are each independently is 0 or 1;

R_{20} is H, C_{1-5} alkyl, C_{1-5} aralkyl, or taken together with R_{18} forms an optionally substituted five-, six-, seven-, or eight-membered heterocyclic ring, having the following structure:



i is 0, 1, 2, 3, 4;

J) an S-sulfonamido of formula



wherein R_{18} is a lower alkyl, lower heteroalkyl, or five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

(1) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

(2) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2, or 3

(3) halogen or perhaloalkyl;

(4) cyano;

(5) nitro;

(6) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and

heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

(7) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl, aryl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

(8) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

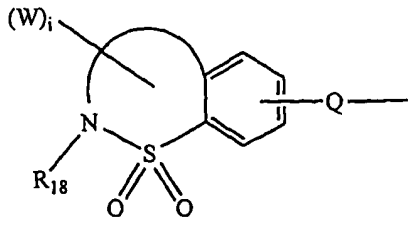
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

wherein R_{19} is H, C_{1-5} alkyl, C_{1-5} aralkyl, or R_{19} taken together with a portion of the ring to which the S of the S-sulfonamido attaches forms an optionally substituted five-, six-, seven-, or eight-membered heterocyclic ring, as shown below:



wherein W is independently selected from the group consisting of

(1) hydrogen;

(2) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

(3) optionally substituted aryl;

(4) optionally substituted heterocyclyl;

(5) an alkoxy of formula $-(X_{13})_{n13}-O-X_{14}$, where

X_{13} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{14} is selected from the group consisting of hydrogen, lower alkyl, aryl, lower perhaloalkyl, and heteroaryl; $n_{13} = 0, 1, 2,$ or 3; and

wherein i is 0, 1, 2, 3, 4;

iii) an acyl of formula $-(X_1)_{n1}-C(O)-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, aryl, heteroaryl, hydroxy, alkoxy, amino, and $-NH-X_3$,

where X_3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, amino, and amide; and

n1 is 0, 1, 2 or 3; and

iv) cyano;

v) nitro;

vi) an amino of formula $-(X_{15})_{n15}-NX_{16}X_{17}$, where

X_{15} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_{16} and X_{17}, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n15 is 0 or 1; and

vii) a thioether or thiol of formula $-(X_{22})_{n22}-S-X_{23}$, where

X_{22} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{23} is selected from the group consisting of hydrogen, lower alkyl, lower perfluoralkyl, aryl, and heteroaryl; and

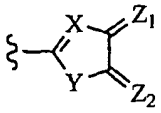
*n*22 is 0, 1, 2, or 3 and

c) R_8 is selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) cyano;

iv) 

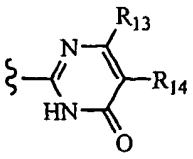
wherein

X is selected from CH and nitrogen;

Y is selected from the group consisting of CH_2, NH, oxygen and sulfur;

Z_1 and Z_2 are each independently selected from the group consisting of null, oxygen, sulfur, and $CR_{11}R_{12}$,

wherein R_{11} and R_{12} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy; and

v) 

wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy;

vi) optionally substituted acyl of the formula $-OC(O)R_E$, wherein $HOC(O)R_E$ is a pharmaceutically acceptable acid;.

d) R_6 and R_7 are each independently selected from the group consisting of hydrogen and lower alkyl.

[0062] In certain embodiments, R_{15} and R16 are independently selected from the group consisting of an optionally substituted five-, six-, seven-, or eight- membered carbocyclic or heterocyclic ring, five-membered or six-membered heteroaryl ring, or six-membered aryl or heteroaryl ring.

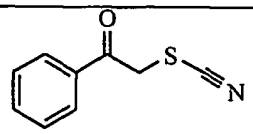
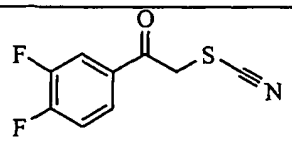
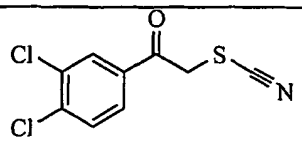
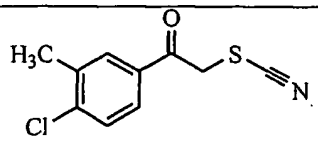
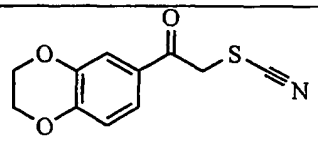
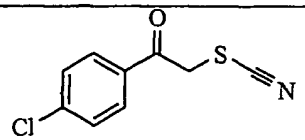
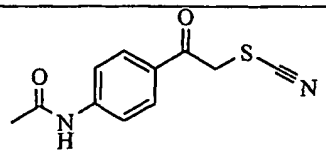
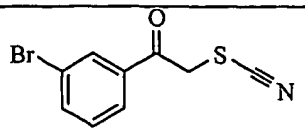
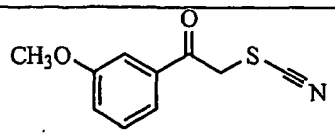
[0063] In some embodiments, R_{16} is selected from the group consisting of hydrogen, lower alkyl, and aryl.

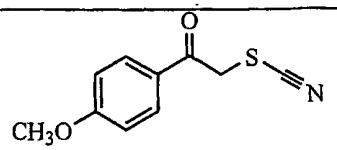
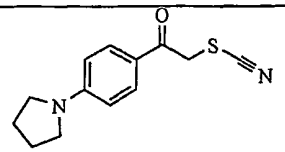
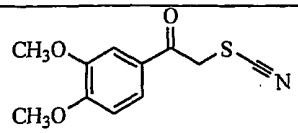
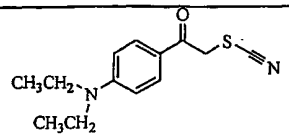
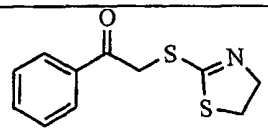
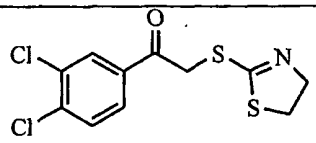
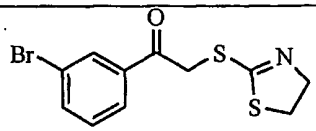
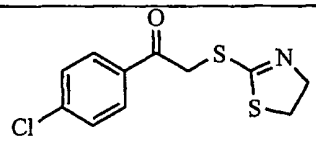
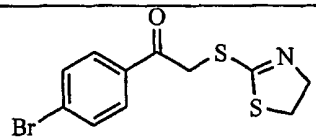
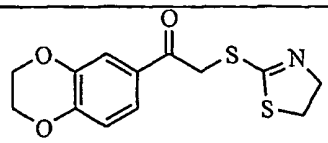
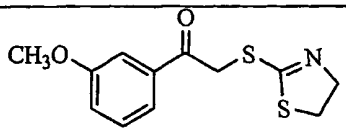
[0064] In certain embodiments, the present invention relates to a compound of Formula II or III where T is sulfur. In other embodiments, T is oxygen, whereas in yet other embodiments, T is -NR.

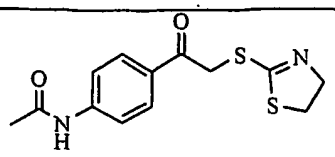
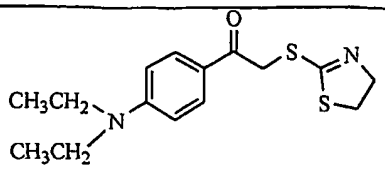
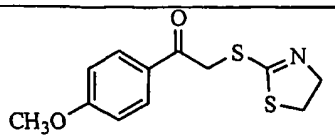
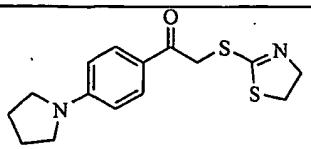
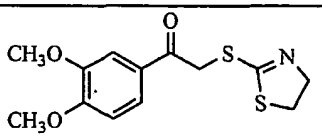
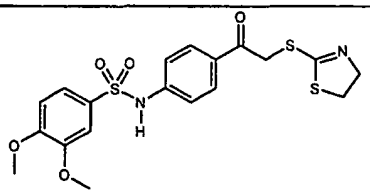
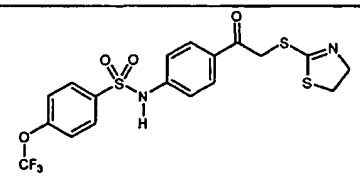
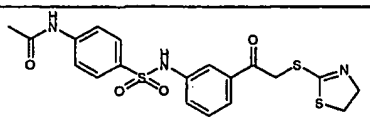
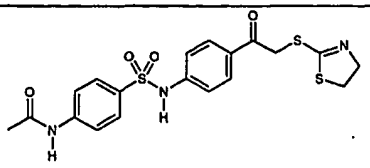
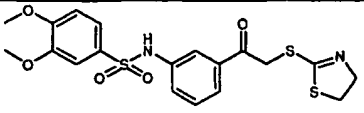
[0065] In another aspect, the invention relates to a compound selected from the group consisting of the compounds set forth in Table 1, or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof:

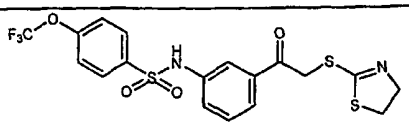
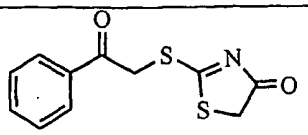
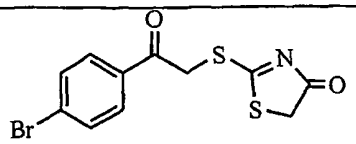
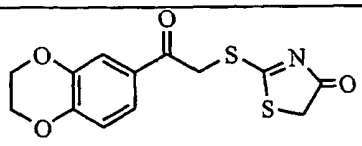
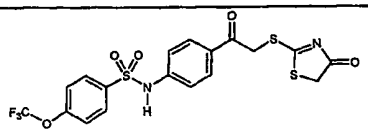
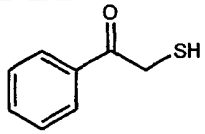
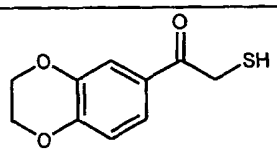
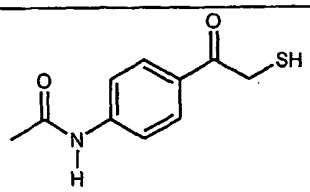
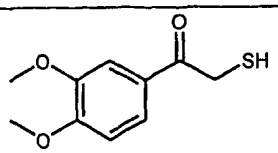
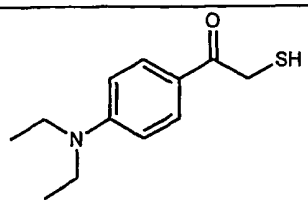
Table 1

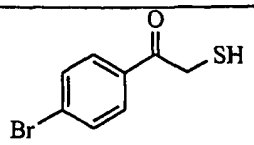
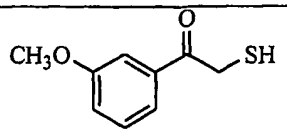
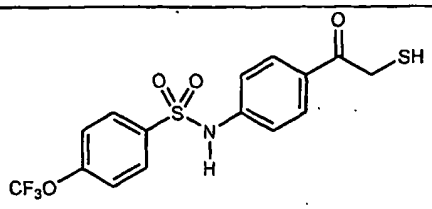
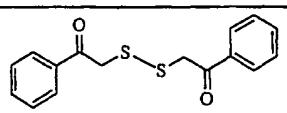
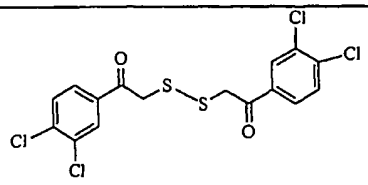
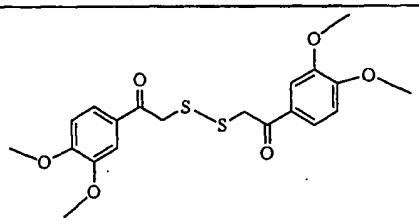
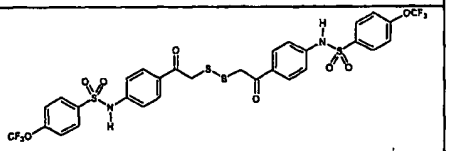
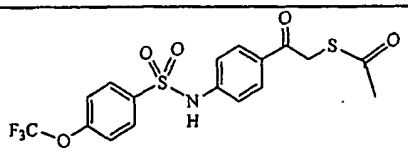
Table 1

Comp'd No.	Structure
1	
2	
3	
4	
5	
6	
7	
8	
9	

10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

21	
22	
23	
24	
25	
26	
27	
28	
29	
30	

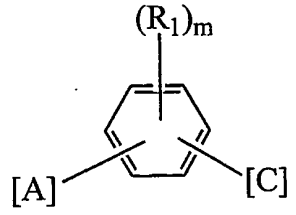
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	

41	
42	
43	
44	
45	
46	
47	
48	

[0066] In another aspect, the present invention is directed to a compound of Formula I, II, or III, as defined herein, including those in Table 1, where the compound is capable of inhibiting the catalytic activity of histone deacetylase (HDAC).

[0067] Another aspect of the present invention are compounds containing at least one thiol in a protected form, which can be released to provide a SH group prior to or simultaneous to use. Thiol moieties are known to be unstable in the presence of air and are oxidized to the corresponding disulfide. Protected thiol groups are those that can be converted under mild conditions into free thiol groups without other undesired side reactions taking place. Suitable thiol protecting groups include but are not limited to trityl (Trt), allyloxycarbonyl (Alloc), 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl (Dde), acetamidomethyl (Acm), t-butyl (tBu), or the like. Preferred thiol protecting groups include lower alkanoyl, e.g. acetyl. Free thiol, disulfides, and protected thiols are understood to be within the scope of this invention.

[0068] Another embodiment of the invention is compounds of Formula IV,

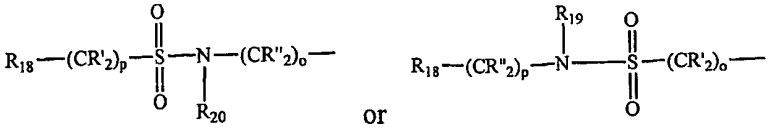


(IV)

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof, or a pharmaceutical composition comprising such compounds and a pharmaceutically acceptable carrier, diluent or excipient,

wherein

a) A is



wherein R_{18} is a lower alkyl, lower heteroalkyl, or five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

i) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

ii) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2 or 3;

iii) halogen, partially halogenated alkyl, or perhaloalkyl;

iv) cyano;

v) nitro;

vi) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

vii) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, perfluoroalkyl, aryl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

viii) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

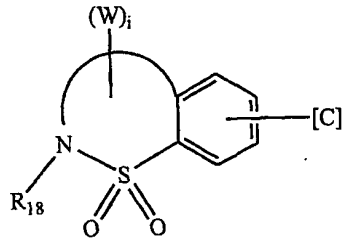
X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, lower heteroalkyl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, lower heteroalkyl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

R' and R" are each independently selected from the group consisting of hydrogen and lower alkyl;

Wherein R_{19} is H, C_{1-5} alkyl, or R_{19} taken together with R^1 forms a five-, six-, seven-, or eight-membered heterocyclic ring, o is 0, and the compound of formula IV has the following structure:



and W is independently selected from the group consisting of

A) hydrogen;

B) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

C) optionally substituted aryl;

D) optionally substituted heterocyclyl;

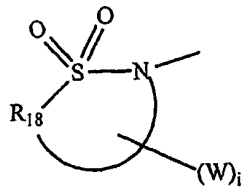
E) an alkoxy of formula $-(X_{13})_{n13}-O-X_{14}$, where

X_{13} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{14} is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; n_{13} = 0, 1, 2, or 3; and

i is 0, 1, 2, 3, 4;

wherein R_{20} is H, C_{1-5} alkyl, or R_{20} taken together with R_{18} forms a five-, six-, seven-, or eight-membered heterocyclic ring, having the following structure:



b) wherein each R_1 is each independently selected from the group consisting of

i) hydrogen;

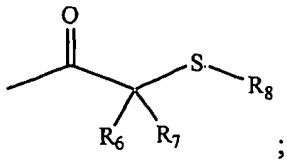
ii) lower alkyl;

iii) lower alkylene;

iv) halogen, partially halogenated alkyl, or perhaloalkyl;

v) an alkoxy or perhaloalkoxy;

c) wherein [C] is



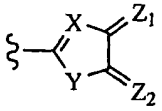
;

d) R_8 is selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) cyano;

iv) 

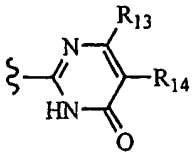
wherein

X is selected from CH and nitrogen;

Y is selected from the group consisting of CH_2, NH, oxygen and sulfur;

Z_1 and Z_2 are each independently selected from the group consisting of null, oxygen, sulfur, and $CR_{11}R_{12}$,

wherein R_{11} and R_{12} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy; and

v) 

wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy;

vi) optionally substituted acyl of the formula -OC(O)R_E, wherein HOC(O)R_E is a pharmaceutically acceptable acid

vii) or R_8 is equivalent to the balance of Formula IV to form a disulfide dimer;

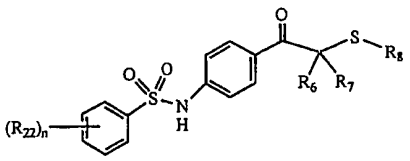
e) R_6 and R_7 are each independently selected from the group consisting of hydrogen and lower alkyl.

[0069] In another aspect are compounds having structural Formula IV wherein R_{19} and R_{20} are each independently H or C_{1-5} alkyl, and o and p are 0.

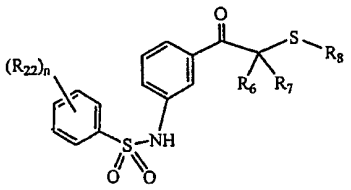
[0070] In another aspect are compounds having structural Formula IV wherein R_{18} is optionally substituted phenyl.

[0071] In another aspect are compounds having structural Formula IV wherein said R_8 forms a pharmaceutically acceptable acid upon thioester hydrolysis. Representaive acids include N,N-diethylglycine; 4-ethylpiperazinoacetic acid; ethyl 2-methoxy-2-phenylacetic acid; N,N-dimethylglycine; (nitrophenoxysulfonyl)benzoic acid, acetic acid, maleic acid, fumaric acid, benzoic acid, tartraric acid, glutamic acid, aspartic acid, proline, D-amino acids, butyric acid, palmitic acid, stearic acid, oleaic acid, pipecolic acid, phosphonic acid, phosphoric acid, pivalate (trimethylacetic acid), succinic acid, cinnamic acid, anthranilic acid, salicylic acid, lactic acid, and, pyruvic acids.

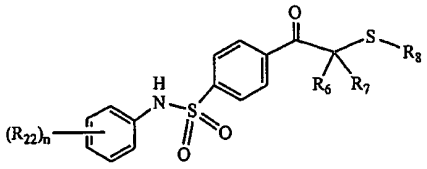
[0072] In another aspect are compounds having structural Formulae V or VI, VII, or VIII:



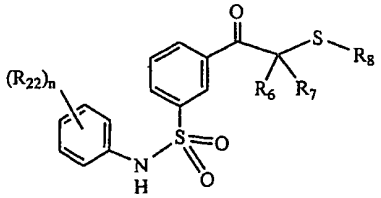
(V)



(VI)



(VII)



(VIII)

wherein

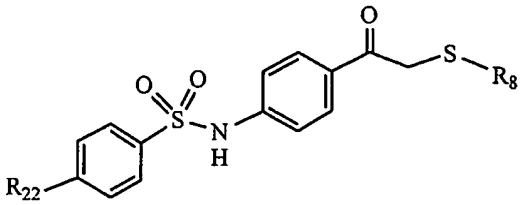
a) R_6 and R_7 are each independently selected from the group consisting of hydrogen and lower alkyl;

b) R_8 is selected from the group consisting of H, acyl, and heterocyclyl;

c) R_{22} is selected from the group consisting of C_{1-5} alkyl, C_{1-5} perhaloalkyl, C_{1-5} alkoxy, C_{1-5} perhaloalkyl alkoxy, and N-alkylamido;

d) n = 0, 1, 2, 3.

[0073] In another aspect are compounds having structural Formula:



and wherein R_{22} is C_{1-5} perfluoroalkyl and R_8 is a thiol protecting group as described herein.

[0074] In another aspect are compounds or compositions comprising compounds capable of inhibiting the catalytic activity of histone deacetylase (HDAC).

[0075] In some aspects of the invention, the disease to be treated by the methods of the present invention may be cancer. In some embodiments, but without limitation, the term cancer refers to and is selected from disorders such as colon cancer, breast cancer, ovarian cancer, lung cancer and prostrate cancer, tumor invasion, tumor growth, tumor metastasis, and cancers of the oral cavity and pharynx (lip, tongue, mouth, pharynx), esophagus, stomach, small intestine, large intestine, rectum, liver and biliary passages, pancreas, larynx, bone, connective tissue, skin, cervix uteri, corpus endometrium, testis, bladder, kidney and other urinary tissues, eye, brain and central nervous system, thyroid and endocrine gland. The term "cancer" also encompasses Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma and hematopoietic malignancies including leukemias (Chronic Lymphocytic Leukemia) and lymphomas including lymphocytic, granulocytic and monocytic.

[0076] Additional types of cancers which may be treated using the compounds and methods described herein include: adrenocarcinoma, angiosarcoma, astrocytoma, acoustic neuroma, anaplastic astrocytoma, basal cell carcinoma, blastoglioma, chondrosarcoma, choriocarcinoma, chordoma, craniopharyngioma, cutaneous melanoma, cystadenocarcinoma, endotheliosarcoma, embryonal carcinoma, ependymoma, Ewing's tumor, epithelial carcinoma, fibrosarcoma, gastric cancer, genitourinary tract cancers, glioblastoma multiforme, head and neck cancer, hemangioblastoma, hepatocellular carcinoma, hepatoma, Kaposi's sarcoma, large cell carcinoma, cancer of the larynx, leiomyosarcoma, leukemias, liposarcoma, lymphatic system cancer, lymphomas, lymphangiosarcoma, lymphangioendotheliosarcoma, medullary thyroid carcinoma,

medulloblastoma, meningioma mesothelioma, myelomas, myxosarcoma neuroblastoma, neurofibrosarcoma, oligodendroglioma, osteogenic sarcoma, epithelial ovarian cancer, papillary carcinoma, papillary adenocarcinomas, parathyroid tumours, pheochromocytoma, pinealoma, plasmacytomas, retinoblastoma, rhabdomyosarcoma, sebaceous gland carcinoma, seminoma, skin cancers, melanoma, small cell lung carcinoma, squamous cell carcinoma, sweat gland carcinoma, synovioma, thyroid cancer, uveal melanoma, and Wilm's tumor

[0077] In some aspects of the invention, the disease to be treated by the methods of the present invention may be a neurological or polyglutamine-repeat disorder. In some embodiments, but without limitation, the polyglutamine-repeat disorder is selected from Huntington's disease, Spinocerebellar ataxia 1 (SCA 1), Machado-Joseph disease (MJD)/Spinocerebella ataxia 3 (SCA 3), Kennedy disease/Spinal and bulbar muscular atrophy (SBMA) and Dentatorubral pallidolusyian atrophy (DRPLA).

[0078] In some aspects of the invention, the disease to be treated by the methods of the present invention may be an anemias or thalassemia (such as Sickle Cell Disease (SCD). In some embodiments, but without limitation, the thalassemia is Sickle Cell Disease (SCD).

[0079] In some aspects of the invention, the disease to be treated by the methods of the present invention may be an inflammatory condition. In some embodiments, but without limitation, the inflammatory condition is selected from Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD), ulcerative colitis and psoriasis.

[0080] In some aspects of the invention, the disease to be treated by the methods of the present invention may be an autoimmune disease. In some embodiments, but without limitation, the autoimmune disease is selected from Systemic Lupus Erythromatosus (SLE) and Multiple Sclerosis (MS).

[0081] In some aspects of the invention, the disease to be treated by the methods of the present invention may be a cardiovascular condition. In some embodiments, but without limitation, the cardiovascular condition is selected from cardiac hypertrophy and heart failure.

[0082] The terms "therapy" or "treating" as used herein refer to (1) reducing the rate of progress of a disease, or, in case of cancer reducing the size of the tumor; (2) inhibiting to some extent further progress of the disease, which in case of cancer may mean slowing to some extent, or preferably stopping, tumor metastasis or tumor growth; and/or, (3) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with

the disease. Thus, the term "therapeutically effective amount" as used herein refers to that amount of the compound being administered which will provide therapy or affect treatment.

[0083] In some aspects of the invention, the compounds of the present invention are also anti-tumor compounds and/or inhibit the growth of a tumor, i.e., they are tumor-growth-inhibiting compounds. The terms "anti-tumor" and "tumor-growth-inhibiting," when modifying the term "compound," and the terms "inhibiting" and "reducing", when modifying the terms "compound" and/or "tumor," mean that the presence of the subject compound is correlated with at least the slowing of the rate of growth of the tumor. More preferably, the terms "anti-tumor," "tumor-growth-inhibiting," "inhibiting," and "reducing" refer to a correlation between the presence of the subject compound and at least the temporary cessation of tumor growth. The terms "anti-tumor," "tumor-growth-inhibiting," "inhibiting," and "reducing" also refer to, a correlation between the presence of the subject compound and at least the temporary reduction in the mass of the tumor.

[0084] The term "function" refers to the cellular role of HDAC. The term "catalytic activity", in the context of the invention, defines the rate at which HDAC deacetylates a substrate. Catalytic activity can be measured, for example, by determining the amount of a substrate converted to a product as a function of time. Deacetylation of a substrate occurs at the active-site of HDAC. The active-site is normally a cavity in which the substrate binds to HDAC and is deacetylated.

[0085] The term "substrate" as used herein refers to a molecule deacetylated by HDAC. The substrate is preferably a peptide and more preferably a protein. In some embodiments, the protein is a histone, whereas in other embodiments, the protein is not a histone.

[0086] The term "activates" refers to increasing the cellular function of HDAC. The term "inhibit" refers to decreasing the cellular function of HDAC. HDAC function is preferably the interaction with a natural binding partner and most preferably catalytic activity.

[0087] The term "modulates" refers to altering the function of HDAC by increasing or decreasing the probability that a complex forms between HDAC and a natural binding partner. A modulator may increase the probability that such a complex forms between HDAC and the natural binding partner, or may increase or decrease the probability that a complex forms between HDAC and the natural binding partner depending on the concentration of the compound exposed to HDAC, or may decrease the probability that a complex forms between HDAC and the natural binding partner. A modulator may activate

the catalytic activity of HDAC, or may activate or inhibit the catalytic activity of HDAC depending on the concentration of the compound exposed to HDAC, or may inhibit the catalytic activity of HDAC.

[0088] The term "complex" refers to an assembly of at least two molecules bound to one another. The term "natural binding partner" refers to polypeptides that bind to HDAC in cells. A change in the interaction between HDAC and a natural binding partner can manifest itself as an increased or decreased probability that the interaction forms, or an increased or decreased concentration of HDAC/natural binding partner complex.

[0089] The term "contacting" as used herein refers to mixing a solution comprising a compound of the invention with a liquid medium bathing the cells of the methods. The solution comprising the compound may also comprise another component, such as dimethylsulfoxide (DMSO), which facilitates the uptake of the compound or compounds into the cells of the methods. The solution comprising the compound of the invention may be added to the medium bathing the cells by utilizing a delivery apparatus, such as a pipet-based device or syringe-based device.

[0090] The term "monitoring" refers to observing the effect of adding the compound to the cells of the method. The effect can be manifested in a change in cell phenotype, cell proliferation, HDAC catalytic activity, substrate protein acetylation levels, gene expression changes, or in the interaction between HDAC and a natural binding partner.

[0091] The term "effect" describes a change or an absence of a change in cell phenotype or cell proliferation. "Effect" can also describe a change or an absence of a change in the catalytic activity of HDAC. "Effect" can also describe a change or an absence of a change in an interaction between HDAC and a natural binding partner.

[0092] The term "cell phenotype" refers to the outward appearance of a cell or tissue or the function of the cell or tissue. Examples of cell phenotype are cell size (reduction or enlargement), cell proliferation (increased or decreased numbers of cells), cell differentiation (a change or absence of a change in cell shape), cell survival, apoptosis (cell death), or the utilization of a metabolic nutrient (e.g., glucose uptake). Changes or the absence of changes in cell phenotype are readily measured by techniques known in the art.

A. Pharmaceutical Compositions

[0093] The present invention also relates to a pharmaceutical composition comprising

a) a compound of the invention, or a pharmaceutically acceptable salt, solvate, amide, ester, or prodrug thereof, as described herein; and

b) a pharmaceutically acceptable carrier, diluent, or excipient, or a combination thereof.

[0094] The term "pharmaceutical composition" refers to a mixture of a compound of the invention with other chemical components, such as carriers, diluents or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0095] The term "carrier" refers to relatively nontoxic chemical compounds or agents. Such carriers may facilitate the incorporation of a compound into cells or tissues. For example, human serum albumin (HSA) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

[0096] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a more stable environment. Salts dissolved in buffered solutions (providing pH control) are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline. It is a buffer found naturally in the blood system. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

[0097] The compounds described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," 20th ed. Edited by Alfonso Gennaro, 2000.

1) Routes Of Administration

[0098] Suitable routes of administration may, for example, include oral, rectal, transmucosal, pulmonary, ophthalmic or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

[0099] Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in

a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

2) Composition/Formulation

[00100] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00101] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[00102] For intravenous injections, the agents of the invention may be formulated in aqueous solutions, preferably in pharmaceutically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, the agents of the invention may be formulated in aqueous or nonaqueous solutions, preferably with pharmaceutically compatible buffers or excipients. Such excipients are generally known in the art.

[00103] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers or excipients well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more compound of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose,

hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00104] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00105] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[00106] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in conventional manner.

[00107] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00108] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[00109] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[00110] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[00111] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[00112] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00113] A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a 10% ethanol, 10% polyethylene glycol 300, 10% polyethylene glycol 40 castor oil (PEG-40 castor oil) with 70% aqueous solution. This cosolvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a cosolvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the cosolvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of PEG-40 castor oil, the fraction size of polyethylene glycol 300 may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides maybe included in the aqueous solution.

[00114] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of

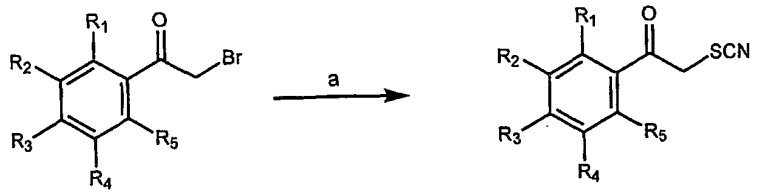
delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as N-methylpyrrolidone also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[00115] Many of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

EXAMPLES

[00116] The examples below are non-limiting and are merely representative of various aspects of the invention.

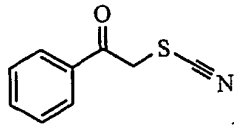
Example 1: General Procedure for the Synthesis of Thiocyanates:



Reagents: (a) NaSCN, EtOH

[00117] Sodium thiocyanide (1 eq.) is dissolved in ethanol (9 mL) before the alpha-bromo ketone (1 eq.) is added as a solid. The resulting solution is then allowed to stir at room temperature for 10 minutes. The volatiles are removed under a stream of nitrogen and the resulting residue is taken up in ethyl acetate before being extracted with water. The organic fraction is dried over Na_2SO_4 and evaporated to leave an oil which is crystallized upon standing. The product is purified by radial chromatography and recrystallized from EtOAc/hexanes.

This general procedure was utilized for the preparation of Compounds 1-13, and is specifically exemplified for Compound 1, below:



Compound 1

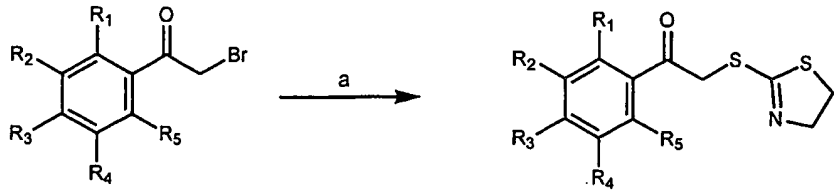
Compound 1: Synthesis of 1-Phenyl-2-thiocyanato-ethanone:

[00118] Sodium thiocyanide (200 mg, 2.47 mmol) was dissolved in ethanol (9 mL) before 1-bromoacetophenone (481 mg, 2.42 mmol) was added as a solid. The resulting tan solution was then allowed to stir at room temperature for 10 minutes. The volatiles were removed under a stream of nitrogen and the resulting residue was taken up in ethyl acetate before being extracted with water. The organic fraction was dried over Na_2SO_4 and evaporated to leave an oil which crystallized upon standing. The product, Compound 1 was

purified by radial chromatography and recrystallized from EtOAc/hexanes (400 mg, 2.26 mmol, 93 %). It had ^{1}H-NMR: ($CDCl_3$) 7.94 (dd, 2H), 7.66 (m, 1H), 7.56 (m, 2H), 4.75 (s, 2H) ppm. It had LCMS (ES+): 91 $[M - C_2NOS]^+$ m/e.

Compounds 2-13 were similarly prepared.

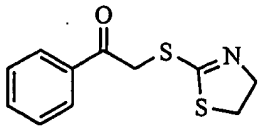
Example 2: General Procedure for the Synthesis of Thiazolines:



Reagents: (a) 2-mercaptothiazoline, NaOH, EtOH

[00119] 2-Mercaptothiazoline (1 eq.) is suspended in ethanol (7 mL) before NaOH (1.8 mL, 2 M) is added affording a clear solution. The alpha-bromo ketone compound (1 eq.) is then added as a solid and the resulting solution is allowed to stir at 40 °C for 3 hours. The volatiles are then removed under a stream of nitrogen before water and EtOAc are added for extraction. The organic layer is dried over Na_2SO_4 and evaporated to leave a dark residue which is purified by radial chromatography. The product is recrystallized from EtOAc/hexanes.

[00120] This general procedure was utilized for the preparation of Compounds 14-31, and is specifically exemplified for Compound 14, with analytical data in support of characterization of Compounds 26, 27, 28 and 29, below:

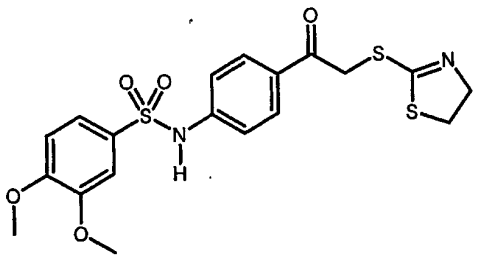


Compound 14

Compound 14: Synthesis of 2-(4,5-Dihydro-thiazol-2-ylsulfanyl)-1-phenyl-ethanone:

[00121] 2-Mercaptothiazoline (300 mg, 2.5 mmol) was suspended in ethanol (7 mL) before NaOH (1.8 ml, 2 M) was added affording a clear solution. 1-Bromoacetophenone (491 mg, 2.47 mmol) was then added as a solid and the resulting red solution was allowed to

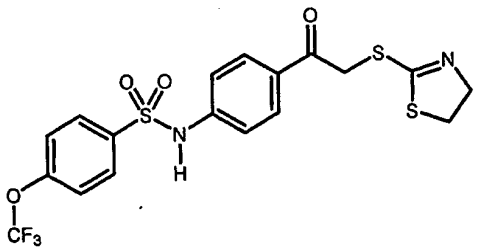
stir at 40 °C for 3 hours. The volatiles were then removed under a stream of nitrogen before water and EtOAc were added for extraction. The organic layer was dried over Na_2SO_4 and evaporated to leave a dark residue which was purified by radial chromatography. The purified product, Compound 14, was recrystallized from EtOAc/hexanes (500 mg, 84 %). It had ^{1}H-NMR: ($CDCl_3$) 8.01 (m, 2H), 7.60 (m, 1H), 7.48 (m, 2H), 4.69 (s, 2H), 4.18 (t, 2H), 3.43 (t, 2H) ppm. It had LCMS (ES+): 238 $[MH]^+$ m/e.



Compound 26

Compound 26: Characterization of N-{4-[2-(4,5-Dihydro-thiazol-2-ylsulfanyl)-acetyl]-phenyl}-3,4-dimethoxy-benzenesulfonamide

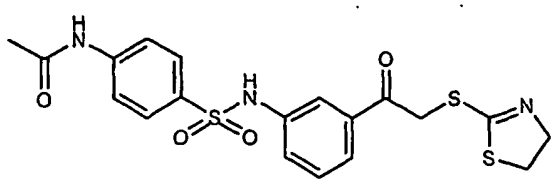
[00122] ^{1}H-NMR: (DMSO-d_6) 10.75 (s, 1H), 7.88 (d, 2H), 7.50 (d, 1H), 7.31 (d, 1H), 7.23 (d, 2H), 7.08 (d, 1H), 4.70 (s, 2H), 4.04 (t, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.43 (t, 2H) ppm. It had LC-MS (ES+): 453 $[M]^+$ m/e.



Compound 27

Compound 27: Characterization of N-{4-[2-(4,5-Dihydro-thiazol-2-ylsulfanyl)-acetyl]-phenyl}-4-trifluoromethoxy-benzenesulfonamide

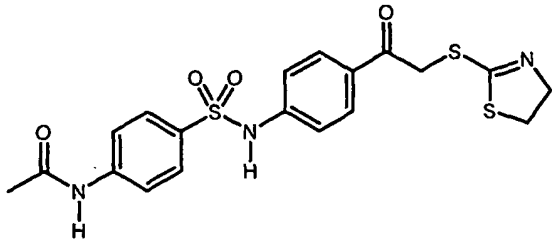
[00123] ^{1}H-NMR: ($CDCl_3$) 7.91 (d, 2H), 7.88 (d, 2H), 7.29 (d, 2H), 7.17 (d, 2H), 6.71 (bs, 1H), 4.59 (s, 2H), 4.16 (t, 2H), 3.43 (t, 2H) ppm. It had LC-MS (ES+): 477 $[M]^+$ m/e.



Compound 28

Compound 28: Characterization of N-(4-{3-[2-(4,5-Dihydro-thiazol-2-ylsulfanyl)-acetyl]-phenylsulfamoyl}-phenyl)-acetamide

[00124] ^{1}H-NMR: (DMSO-d_6) 10.40 (bs, 1H), 10.30 (bs, 1H), 7.70 (m, 6H), 7.30 (m, 2H), 4.70 (s, 1H), 4.1 (t, 2H), 3.50 (t, 2H), 2.00 (s, 3H) ppm. It had LC-MS (ES+): 450 $[M]^+$ m/e.



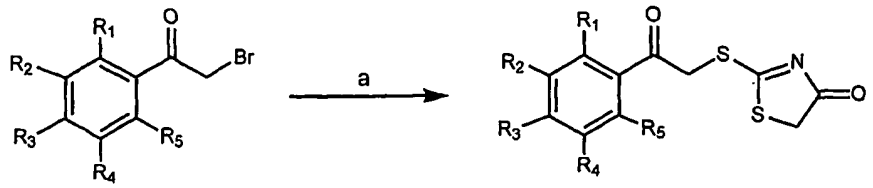
Compound 29

Compound 29: Characterization of N-(4-{4-[2-(4,5-Dihydro-thiazol-2-ylsulfanyl)-acetyl]-phenylsulfamoyl}-phenyl)-acetamide

[00125] ^{1}H-NMR: (DMSO-d_6) 10.80 (bs, 1H), 10.30 (bs, 1H), 7.86 (d, 2H), 7.76 (m, 4H), 7.19 (d, 2H), 4.69 (s, 2H), 4.03 (t, 2H), 3.42 (t, 2H), 2.05 (s, 3H) ppm. It had LC-MS (ES+): 450 $[M]^+$ m/e.

Compounds 15-25, 30 and 31 were similarly prepared.

Example 3: General Procedure for the Synthesis of Thiazolinones:

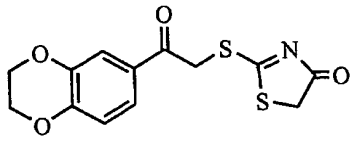


Reagents: a) EtOH, NaOH, Rhodanine

[00126] Rhodanine (1.0 eq.) is dissolved in EtOH (2 mL) and 2 M NaOH (0.275 mL) with vigorous stirring. Once the Rhodanine is completely dissolved, the alpha-

bromo ketone compound (1 eq.) is added with constant stirring. The reaction is mixed overnight at 40°C. After 18 hrs the reaction is removed from the heat and left stirring at room temp for 48 hrs. The resulting reaction mixture is then diluted with water (5 mL) and extracted with dichloromethane (3 x 5 ml). The organic layer is dried over Na_2SO_4 and then evaporated to yield an oil. The oil is purified by chromatotron using a 50/50 mixture of ethyl acetate in hexanes as the mobile phase. The purified product is then recrystallized in hexanes to complete its purification.

[00127] This general procedure was utilized for the preparation of Compounds 32-35, and is specifically exemplified for Compounds 34, below:



Compound 34

Compound 34: Synthesis of 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-oxo-ethylsulfanyl]-thiazol-4-one:

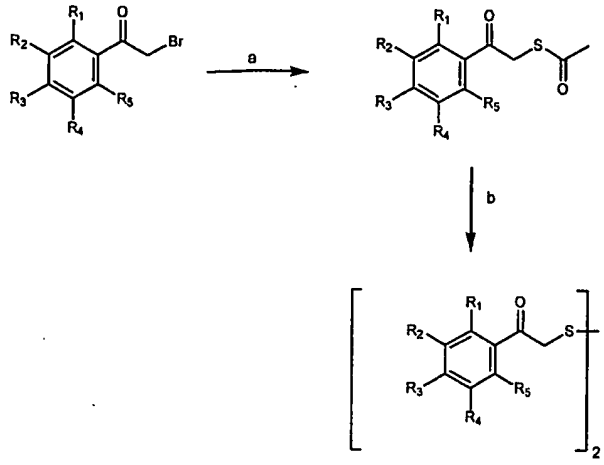
[00128] Rhodanine (0.052 g, 0.388 mmol, 1.0 eq.) was dissolved in EtOH (2ml) and 2 M NaOH (0.275 ml, 0.550 mmol, 1.42 eq.) with vigorous stirring. Once the Rhodanine was completely dissolved, 6-Chloroacetyl-1,4-benzodioxane (0.080 g, 0.380 mmol, 0.98 eq.) was added with constant stirring. (It should be noted that α-chloro ketones were used when the corresponding α-bromo ketones were not available.) The reaction was mixed overnight at 40°C. After 18 hrs the reaction was removed from the heat and left stirring at room temp for 48 hrs. The resulting reaction mixture was then diluted with water (5 ml) and extracted with dichloromethane (3 x 5 ml). The organic layer was dried over Na_2SO_4 and then evaporated to yield an oil. The oil was purified by chromatotron using a 50/50 mixture of ethyl acetate in hexanes as the mobile phase. The purified product, Compound 34, was then recrystallized in hexanes to complete its purification (20mg, 0.0646mmol, 17%). The product was characterized by ^{1}H-NMR: ($CDCl_3$) 7.55 (q, 2H), 6.93 (d, 1H), 4.93 (s, 2H), 4.31 (m, 4H), 4.02 (s, 2H) ppm. In addition LCMS [ES+] analysis yielded a single peak, 310 $[M]^+$ m/e.

Compounds 32, 33 and 35 were similarly prepared.

Example 4: General Procedure for the Synthesis of Mercaptans and Disulfides:

Schemes 1a illustrates the general synthesis of disulfide embodiments of the present invention.

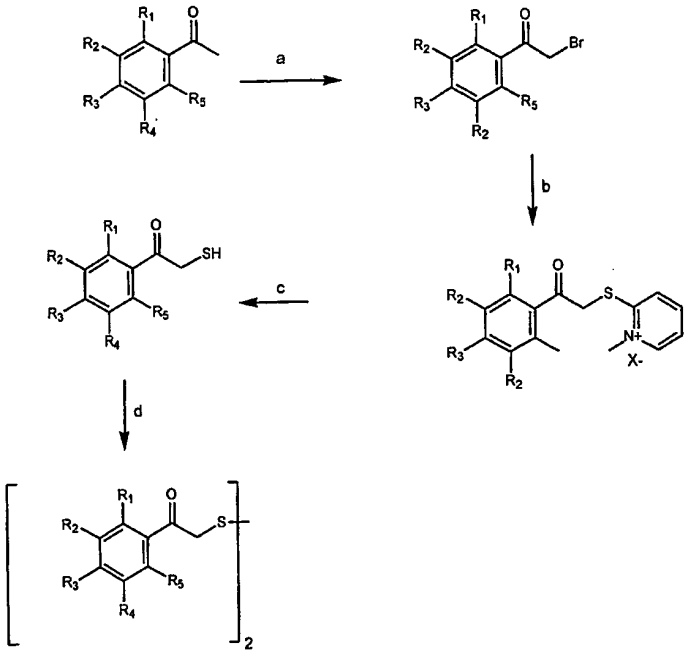
Scheme 1a



Reagents: (a) $KSC(O)CH_3$, MeOH; (b) NaOH, MeOH

Scheme 1b depicts an alternative general scheme for the synthesis of thiol (mercaptan) and disulfide embodiments of the present invention

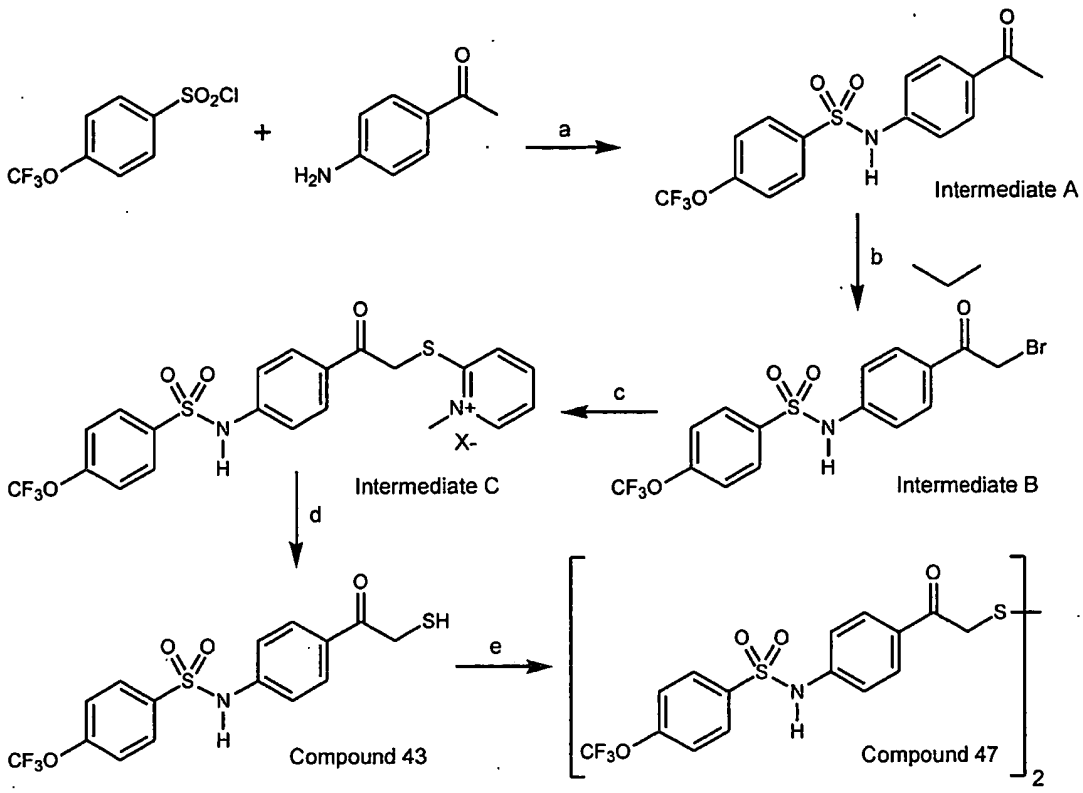
Scheme 1b



Reagents: (a) PTT, THF; (b) N-methyl 2-thiopyridone, EtOH;
(c) NaOH, water; (d) MeOH, water.

Scheme 1c depicts the synthesis of Compound 47, and is exemplary of the general applicability of scheme 1a and 1b to specific alpha-thio ketone and disulfide molecular embodiments of the invention.

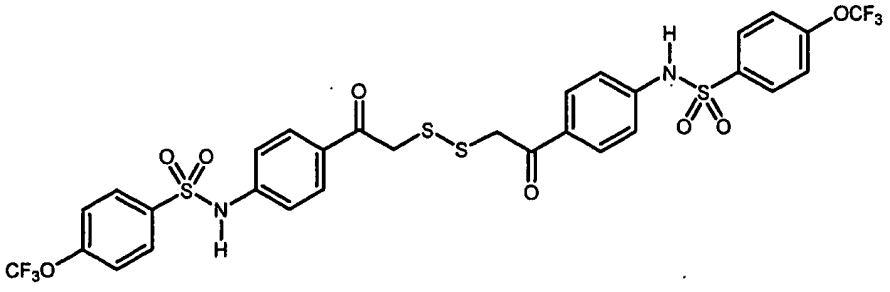
Scheme 1c



Reagents: (a) pyridine, THF; (b) PTT, THF; (c) N-methyl 2-thiopyridone, EtOH; (d) NaOH, water; (e) MeOH, water.

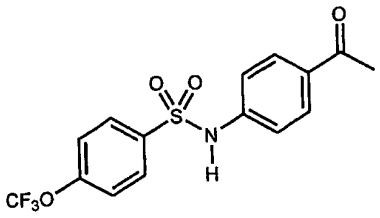
Compound 47: Synthesis of Thioacetic acid *S*-{2-oxo-2-[4-(4-trifluoromethoxy-benzenesulfonylamino)-phenyl]-ethyl} disulfide

[00129]



Compound 47

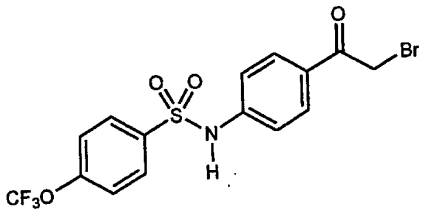
Step 1: Synthesis of Intermediate A



Intermediate A

Intermediate A: Synthesis of N-(4-Acetyl-phenyl)-4-trifluoromethoxy-benzenesulfonamide
4'-Amino acetophenone (0.375 g, 2.78 mmol) was dissolved in THF (5 ml) before pyridine (0.674 ml, 8.34 mmol) was added, leaving a yellow solution. 4-trifluoromethoxy benzenesulfonylchloride (0.871 g, 3.34 mmol) was then added dropwise with stirring. After removal of THF and pyridine, the desired sulfonamide (0.848 g, 2.36 mmol, 85 %) was recrystallized from ethyl acetate and hexanes. ^{1}H-NMR: (400 MHz, $CDCl_3$) 7.89 (m, 4H), 7.29 (d, 1H), 7.16 (d, 2H), 6.88 (s, 1H), 2.55 (s, 3H). LC-MS (ES+): 360 $[MH]^+$ m/e.

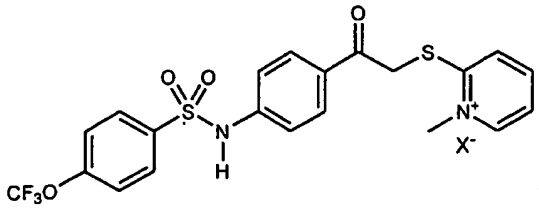
Step 2: Synthesis of Intermediate B



Intermediate B

Intermediate B: Synthesis of N-[4-(2-Bromo-acetyl)-phenyl]-4-trifluoromethoxy-benzenesulfonamide
Intermediate A (0.32 g, 0.868 mmol) was dissolved in THF (9 ml), and phenyltrimethylammonium tribromide (PTT) (0.368 g, 0.868 mmol) was added as a solid leaving an orange solution which began to deposit a white solid immediately. Stirring for 1.5 hours leaves a colorless mixture to which water (5 ml) was added. THF was then evaporated and the resulting aqueous mixture was extracted with ethyl acetate. Drying over Na_2SO_4 and evaporation leaves a white crystalline solid (90% desired mono-brominated material by LC-MS, 5% starting material, 5 % dibrominated) suitable for the next step. LC-MS (ES-): 436, 438 m/e.

Step 3: Synthesis of Intermediate C

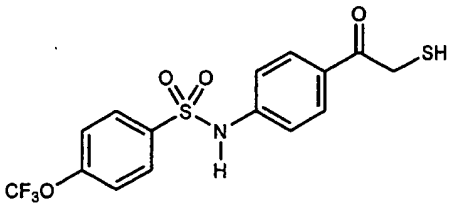


Intermediate C

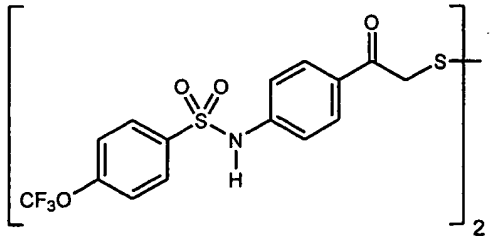
Intermediate C: Synthesis of 1-Methyl-2-{2-oxo-2-[4-(4-trifluoromethoxybenzene-sulphonylamino) phenyl]ethylsulfanyl}-pyridinium bromide

Intermediate B (0.141 g crude material, 0.322 mmol) was dissolved in ethanol (2 ml) before N-methyl thiopyridone (0.040 g, 0.322 mmol) was added as a solid. The resulting yellow solution was then heated to reflux overnight. Evaporation of the volatiles leaves a residue (75 % by NMR, 0.116 g, 0.240 mmol) suitable for the next step, however, the product may be recrystallized from ethanol if desired. ^{1}H-NMR: (400 MHz, DMSO-d_6) 11.21 (s, 1H), 8.90 (d, 1H), 8.18 (t, 1H), 8.03 (m, 5H), 7.90 (t, 1H), 7.80 (d, 2H), 7.15 (d, 2H), 5.33 (s, 2H), 4.24 (s, 3H). LC-MS (ES+): 483 $[M]^+$ m/e.

Steps 4 and 5: Synthesis of Compound 43 and Compound 47



Compound 43



Compound 47

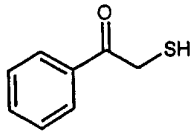
[00130] Compound 43 and Compound 47: Synthesis of N-[4-(2-Mercapto-acetyl)-phenyl]-4-trifluoromethoxy-benzenesulfonamide (43) and corresponding disulfide (47)

Intermediate C (4.35 g, 7.72 mmol) was suspended in water (1.7 l) before 2 M NaOH (7.25 ml) was added. Solid NaOH (1 g) was then added, and the resulting mixture was then heated to reflux overnight, producing a red solution. The solution was then acidified to a pH of 1 and extracted with ethyl acetate. Drying over Na_2SO_4 and evaporation leaves a red oil.

Throughout the work-up, the alpha-mercapto ketone readily oxidizes to the corresponding disulfide (**47**), which was purified by preparative HPLC (0.582 g, 0.75 mmol, 10 %). ^{1}H-NMR: (400 MHz, DMSO-d_6) 11.09 (bs, 2H), 7.97 (d, 4H), 7.85 (d, 4H), 7.57 (d, 4H), 7.22 (d, 4H), 4.29 (s, 4H). LC-MS (ES+): 781 $[MH]^+$ m/e.

[00131] Alpha thioketones Compounds 36-42 and disulfide Compounds 44-46 were similarly prepared.

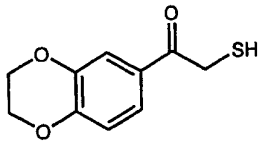
[00132] Analytical data is support of the characterization of Compound 36-41 and Compounds 44-46 are presented below:



Compound 36

Compound 36: Characterization of 2-Mercapto-1-phenyl-ethanone

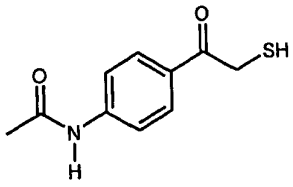
[00133] ^{1}H-NMR: (400 MHz, $CDCl_3$) 7.99 (d, 2H), 7.61 (m, 1H), 7.51 (m, 2H), 3.97 (d, 2H), 2.14 (t, 1H). LC-MS (ES+): 153 $[MH]^+$ m/e.



Compound 37

Compound 37: Characterization of 1-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-mercapto-ethanone

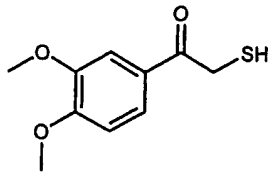
[00134] ^{1}H-NMR: (400 MHz, $CDCl_3$) 7.50 (m, 2H), 6.93 (dd, 1H), 4.31 (m, 4H), 3.88 (d, 2H), 2.13 (t, 1H). LC-MS (ES+): 211 $[MH]^+$ m/e.



Compound 38

Compound 38: Characterization of N-[4-(2-Mercapto-acetyl)-phenyl]-acetamide

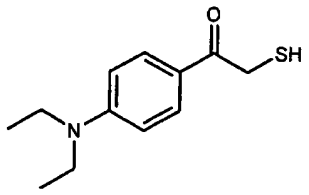
[00135] ^{1}H-NMR: (400 MHz, DMSO-d_6) 10.32 (bs, 1H), 7.95 (d, 2H), 7.72 (d, 2H), 4.02 (d, 2H), 2.84 (t, 1H) 2.09 (s, 3H). LC-MS (ES+): 210 $[MH]^+$ m/e



Compound 39

Compound 39: Characteriation of 1-(3,4-Dimethoxy-phenyl)-2-mercapto-ethanone

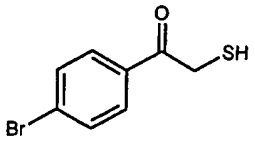
[00136] ^{1}H-NMR: (400 MHz, $CDCl_3$) 7.56 (m, 2H), 6.91 (d, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.92 (d, 2H), 2.15 (t, 1H). LC-MS (ES+): 213 $[MH]^+$ m/e.



Compound 40

Compound 40: Characterization of 1-(4-Diethylamino-phenyl)-2-mercapto-ethanone

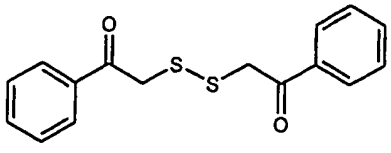
[00137] ^{1}H-NMR: (400 MHz, $CDCl_3$) 7.83 (dd, 2H), 6.63 (dd, 2H), 3.85 (d, 2H), 3.43 (q, 4H), 2.17 (t, 1H), 1.21 (t, 6H). LC-MS (ES+): 224 $[MH]^+$ m/e.



Compound 41

Compound 41: CHaraterization of 1-(4-Bromo-phenyl)-2-mercapto-ethanone

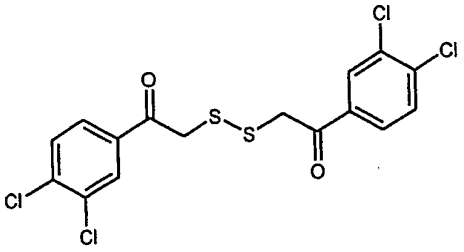
[00138] ^{1}H-NMR: (400 MHz, $CDCl_3$) 7.83 (m, 2H), 7.64 (m, 2H), 3.92 (d, 2H), 2.11 (t, 1H). LC-MS (ES+): 230, 232 $[MH]^+$ m/e.



Compound 44

Compound 44: Synthesis of 2-(2-Oxo-2-phenyl-ethyldisulfanyl)-1-phenyl-ethanone

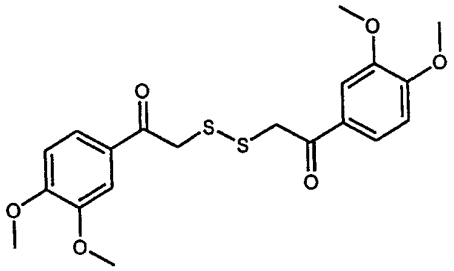
[00139] ^{1}H-NMR: (400 MHz, $CDCl_3$) 7.95 (d, 4H), 7.61 (t, 2H), 7.49 (t, 4H), 4.22 (s, 4H). LC-MS (ES+): 303 $[MH]^+$ m/e.



Compound 45

Compound 45: Synthesis of 1-(3,4-Dichloro-phenyl)-2-[2-(3,4-dichloro-phenyl)-2-oxo-ethyldisulfanyl]-ethanone

[00140] ^{1}H-NMR: (400 MHz, $CDCl_3$) 8.03 (d, 2H), 7.76 (dd, 2H), 7.56 (d, 2H), 4.13 (s, 4H), 7.22 (d, 4H), 4.29 (s, 4H). LC-MS (ES+): 436 $[MH]^+$ m/e.



Compound 46

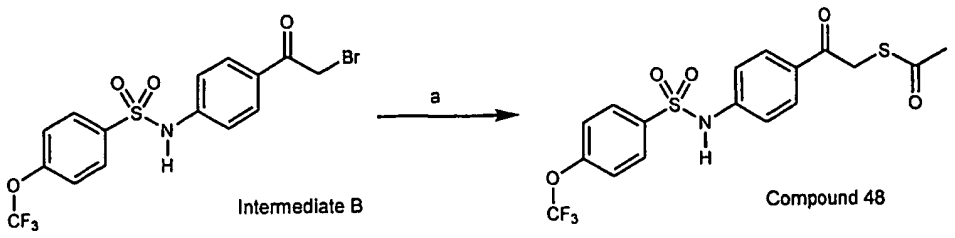
Compound 46: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[2-(3,4-dimethoxy-phenyl)2-oxo-ethyldisulfanyl]-ethanone

[00141] ^{1}H-NMR: (400 MHz, $CDCl_3$) 7.55 (m, 4H), 6.87 (d, 2H), 4.15 (s, 4H), 3.95 (s, 6H), 3.94 (s, 6H). LC-MS (ES+): 423 $[MH]^+$ m/e.

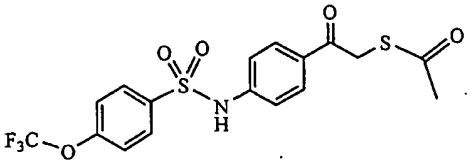
Example 5: General Procedure for the Synthesis of Thioesters and an Alternate General Synthesis of Disulfides:

Scheme 2 outlines a general synthesis of thioesters, explicitly exemplified with reference to the preparation of Compound 48. Hydrolysis of thioesters, followed by oxidation, results in a general synthesis of disulfides, explicitly exemplified with reference to the preparation of Compound 47.

Scheme 2



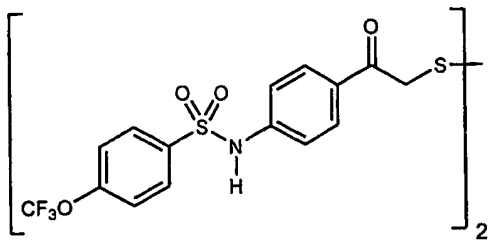
Reagents: a) MeOH, potassium thioacetate



Compound 48

Compound 48: Thioacetic acid S-{2-oxo-2-[4-(4-trifluoromethoxy-benzenesulfonylamino)-phenyl]-ethyl} ester

[00142] Intermediate B (29 g crude material, 66.18 mmol) was dissolved in methanol (500 ml) before potassium thioacetate (8.23 g, 72.06 mmol) was added as a solid. LC-MS of the resulting yellow solution shows the reaction is complete in minutes. Evaporation of the volatiles leaves a tan residue which was taken up into dichloromethane (100 ml), during which a deposit of disulfide (thioacetic acid) was deposited and filtered. The desired thioester could then be recrystallized from dichloromethane/hexanes (18.52 g, 42.67 mmol, 64 %) It had ^{1}H-NMR: (DMSO-d_6) 11.09 (bs, 1H), 7.98 (d, 2H), 7.92 (d, 2H), 7.59 (d, 2H), 7.24 (d, 2H), 4.42 (s, 2H), 2.36 (s, 3H) ppm. It had LC-MS (ES+): 434 $[M]^+$ m/e.



Compound 47

[00143] Compound 47: Corresponding disulfide of Compound 43

[00144] Compound 48 (2.3 g, 5.3 mmol) was dissolved in MeOH (50 ml) before solid NaOH was carefully added with vigorous stirring. The resulting yellow solution was then stirred for 2 hours before being neutralized with con. HCl and evaporated to leave a red residue. Water (20 ml) was added and the mixture extracted with EtOAc. The organic

fractions were dried over Na_2SO_4 and evaporated. The residue was taken up in CH_2Cl_2 (50 ml) and stirred while open to the air. The desired disulfide precipitates within hours and is complete overnight yielding a pure solid (1.1 g, 1.41 mmol, 53 %). It had identical spectral characteristics as the material obtained in the original synthesis.

Example 9: Inhibition Assays:

In vitro HDAC-inhibition Assay:

[00145] This assay measures a compound's ability to inhibit acetyl-lysine deacetylation *in vitro* and was used as both a primary screening method as well as for IC_{50} determinations of confirmed inhibitors. The assay is performed *in vitro* using an HDAC enzyme source (e.g. partially purified nuclear extract or immunopurified HDAC complexes) and a proprietary fluorescent substrate / developer system (HDAC Quantizyme *Fluor de Lys* Fluorescent Activity Assay, BIOMOL). The assay is run in 1,536-well Greiner white-bottom plates using the following volumes and order of addition:

[00146] Step 1: Enzyme (2.5 ul) source added to plate (from refrigerated container)

Step 2: Compounds (50 nl) added with pin transfer device

Step 3: *Fluor de Lys* (2.5 ul) substrate added, incubate at RT, 30 minutes

Step 4: Developer (5 ul) solution is added (containing TSA), to stop reaction

Step 5: Plate Reader - data collection

[00147] The deacetylated fluorophore is excited with 360 *nm* light and the emitted light (460 *nm*) is detected on an automated fluorometric plate reader (Aquest, *Molecular Devices*).

Cellular Histone Hyperacetylation Assays:

[00148] These two secondary assays evaluates a compound's ability to inhibit HDAC in cells by measuring cellular histone acetylation levels. The cytoblot facilitates quantitative EC_{50} information for cellular HDAC inhibition. Transformed cell lines (e.g. HeLa, A549, MCF-7) are cultured under standard media and culture conditions prior to plating.

For Cytoblot:

[00149] Cells (approx. 2,500/well) are allowed to adhere 10-24 hours to wells of a 384-well Greiner PS assay plate in media containing 1-5% serum. Cells are treated with appropriate compound and specific concentrations for 0 to 24 hours. Cells are washed once with PBS (60 ul) and then fixed (95% ethanol, 5% acetic acid or 2% PFA) for 1 minute at RT (30 ul). Cells are blocked with 1% BSA for 1 hour and washed and stained with antibody (e.g. anti-Acetylated Histone H3, *Upstate Biotechnology*), followed by washing and incubation with an appropriate secondary antibody conjugated to HRP or fluorophore. For luminescence assays, signal is generated using Luminol substrate (*Santa Cruz Biotechnology*) and detected using an Aquest plate reader (*Molecular Devices*).

For Immunoblot:

[00150] Cells (4 x 10^5/well) are plated into Corning 6-well dish and allowed to adhere overnight. Cells are treated with compound at appropriate concentration for 12-18 hours at 37 degrees. Cells are washed with PBS on ice. Cells are dislodged with rubber policeman and lysed in buffer containing 25 mM Tris, pH7.6; 150 mM NaCl, 25 mM $MgCl_2$, 1% Tween-20, and nuclei collected by centriguation (7500g). Nuclei are washed once in 25 mM Tris, pH7.6; 10 mM EDTA, collected by centrifugation (7500g). Supernatant is removed and histones are extracted using 0.4 M HCl. Samples are centrifuged at 14000g and supernatants are precipitated in 1 ml cold acetone. The histone pellet is dissolved in water and histones are separated and analyzed by SDS-PAGE Coomassie and immunobloting (anti-acetylated histone antibodies, *Upstate Biotechnology*) using standard techniques.

Differential Cytotoxicity Assay:

[00151] HDAC inhibitors display differential cytotoxicity toward certain transformed cell lines. Cells are cultured according to standard ATCC recommended conditions that are appropriate to each cell type. Compounds were tested for their ability to kill different cell types (normal and transformed) using the **ATPlite** luminescence ATP detection assay system (*Perkin Elmer*). Assays are run in either 384-well or 1536-well Greiner PS plates. Cells (30 ul or 5 ul, respectively) are dispensed using either multichannel pipette for 384-well plates, or proprietary *Kalypsys* bulk liquid dispenser for 1536-well plates. Compounds added using proprietary pin-transfer device (500 nL or 5 nL) and incubated 5 to 30 hours prior to analysis. Luminescence is measured using Aquest plate reader (*Molecular Devices*).

[00152] The activity of some of the compounds of the invention are shown in Table 2, below, together with data for positive controls: TSA, HC-toxin, Dioxothiophene & MS-275.

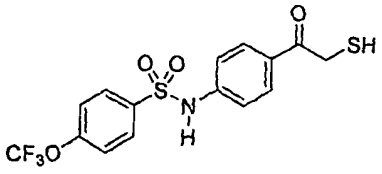
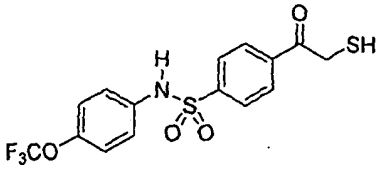
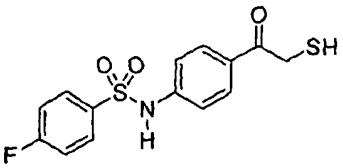
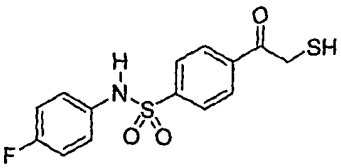
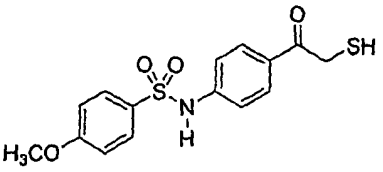
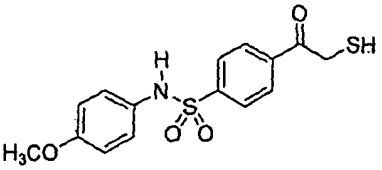
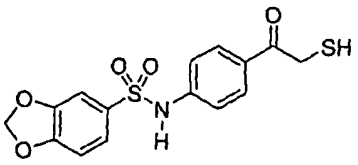
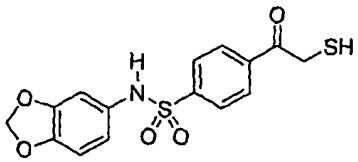
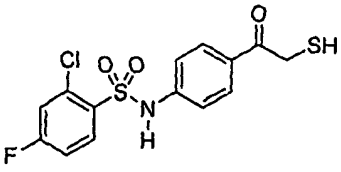
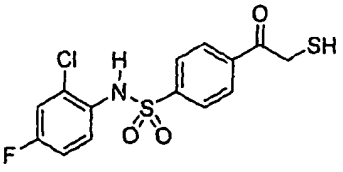
Table 2

Compound Description	in vitro IC_{50} (μM)	%.Max Inhibition (in vitro)	Cellular IC_{50} (μM)	% Max Inhibition (cellular)
TSA positive control (published in vitro IC_{50} = 3 - 6 nM)	<1	100	<1	100
HC-toxin positive control (published in vitro IC_{50} = 7-10 nM)	<1	>75	N.D.	N.D.
Dioxothiophene*	>10	<50	N.D.	N.D.
MS-275 (clinical compound - benzamide anilide)	>10	>50	1-10	>75
1	1-10	>75	active	N.D.
2	<1	>75	active	N.D.
3	<1	>75	1-10	104
4	<1	>75	1-10	>75
5	<1	>75	active	N.D.
6	<1	>75	1-10	>75
7	<1	>75	1-10	>75
8	<1	>75	active	N.D.
9	<1	>75	active	N.D.
10	1-10	>75	active	N.D.
11	1-10	>50	active	N.D.
12	1-10	>75	N.D.	N.D.
13	1-10	>75	active	N.D.
14	>10	>75	>10	<50
15	1-10	>75	1-10	>75
16	1-10	>75	active	N.D.
17	>10	>75	active	N.D.
18	>10	>75	active	N.D.
19	>10	>75	1-10	>50
20	>10	>75	active	N.D.
21	>10	>75	1-10	>75
22	>10	<50	1-10	<50
23	>10	>50	active	N.D.
24	>10	>50	active	N.D.
25	>10	<50	active	N.D.
26	1-10	>75	<1	>75
27	1-10	>75	1-10	>75
29	1-10	>75	1-10	>75
30	1-10	>75	1-10	>75
31	1-10	>75	1-10	>75
32	<1	>75	>10	>50
33	<1	>75	>10	>75
34	<1	>75	1-10	>75
41	<1	>75	active	>75
42	1-10	>75	>10	>75

Compound Description	in vitro IC_{50} (μM)	% Max Inhibition (in vitro)	Cellular IC_{50} (μM)	% Max. Inhibition (cellular)
47	<1	>75	<1	>75
48	<1	>75	<1	>75

"N.D." indicates not determined because max inhibition was not reached at highest concentration tested. "Active" means the compound showed inhibitory activity but the cellular IC_{50} could not be determined

[00153] Exemplary compounds and pharmaceutically acceptable esters or prodrugs thereof according to the invention include, but are not limited to, illustrative disulfide dimers, mercaptans, and thioesters as shown herein. Exemplary mercaptans of compounds according to structures I, II, or IV include the following:

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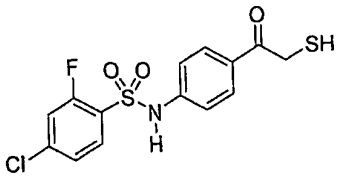
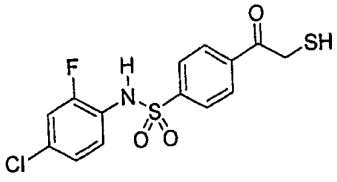
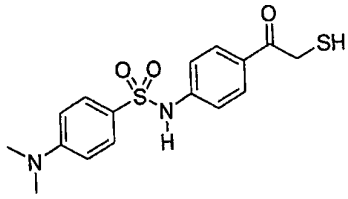
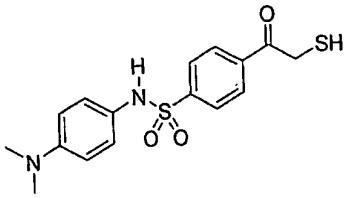
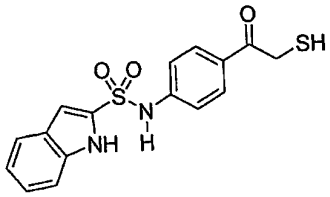
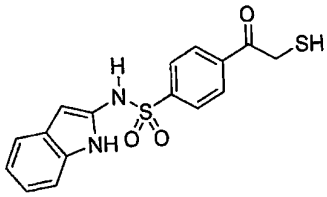


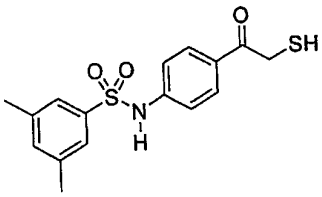


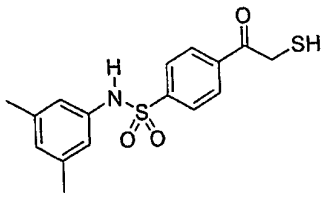


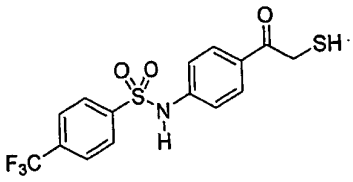


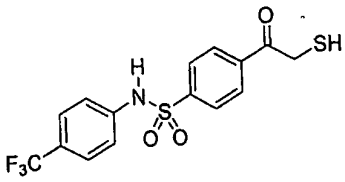


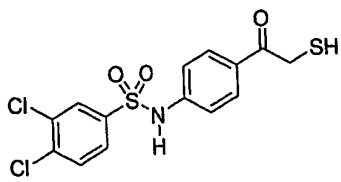


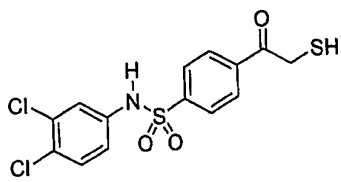


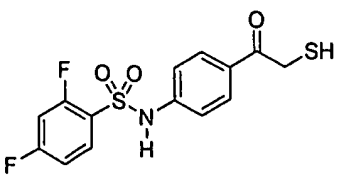
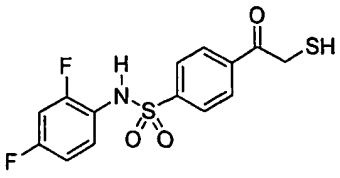
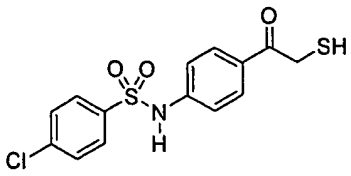
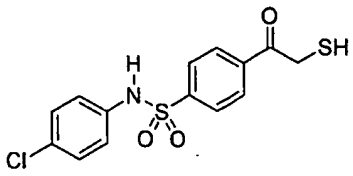
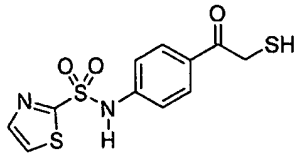
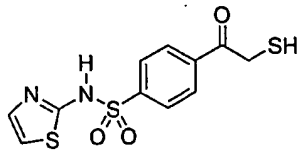
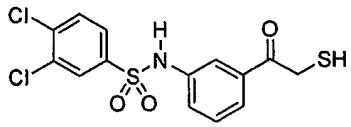
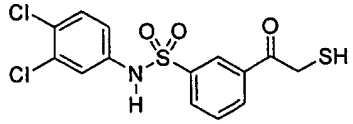
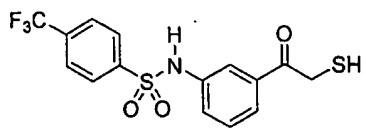
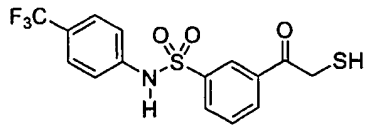
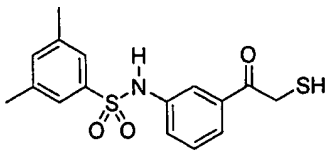
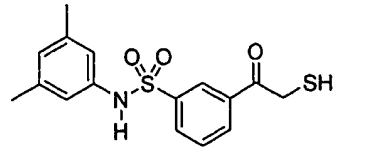
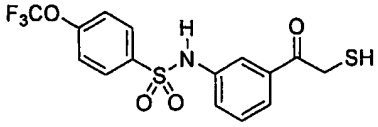
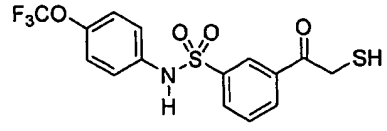






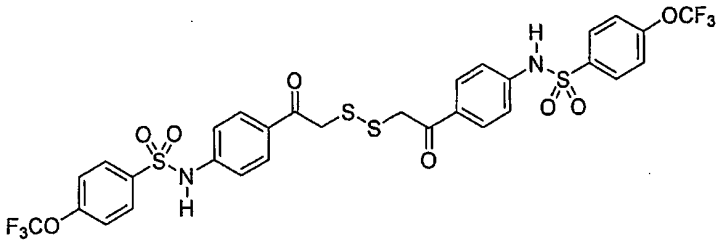


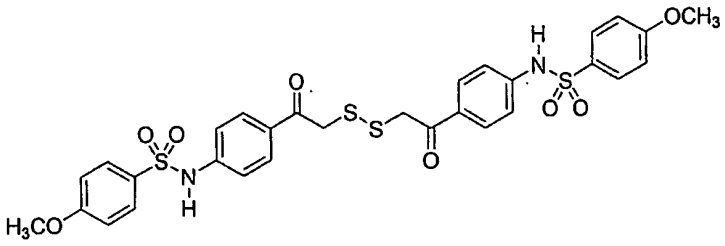


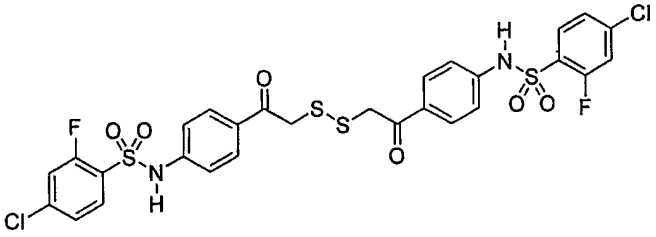















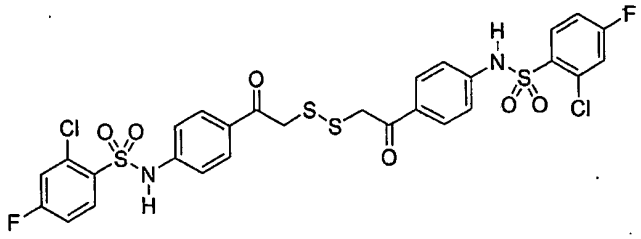
[00154] Preferred disulfides are symmetric and in a preferred embodiment, compounds of structure III are provided by the invention wherein T=S, all R6 are equivalent, all R7 are equivalent, and R15 =R16 or compounds of structure IV wherein R8 is defined so

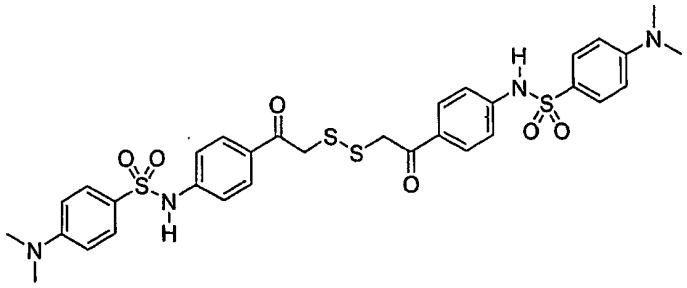
as to form a symmetric disulfide dimer. Exemplary disulfides according to structures I, III, and IV include the following:

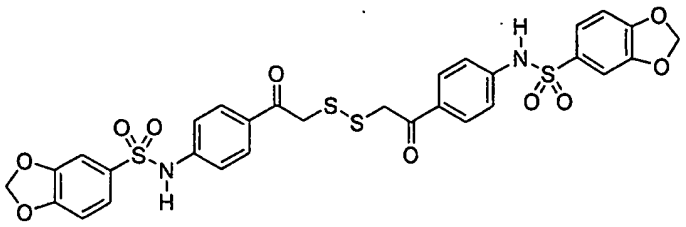


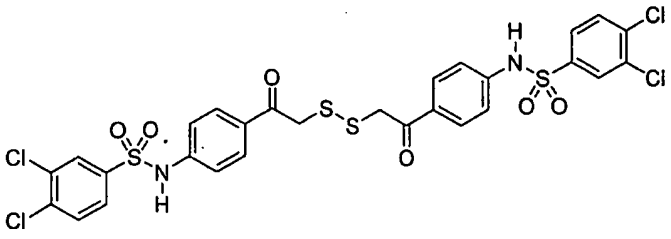


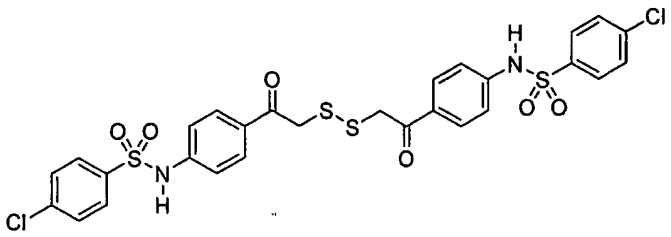


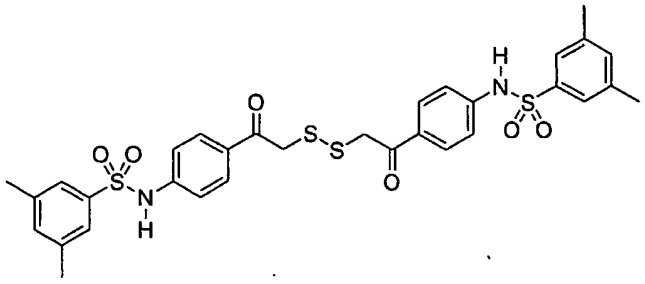


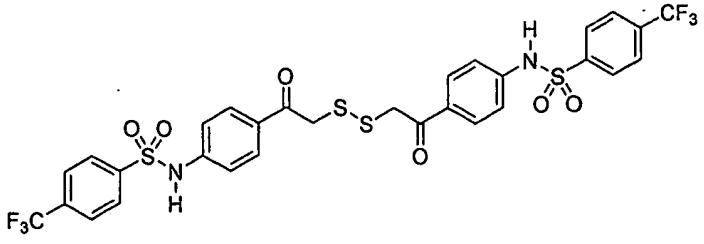


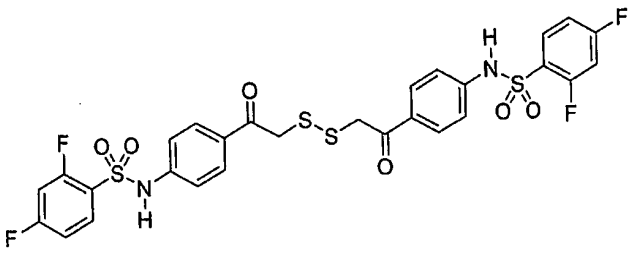


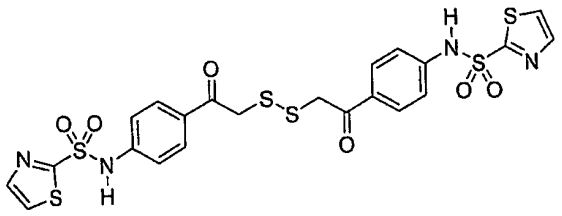


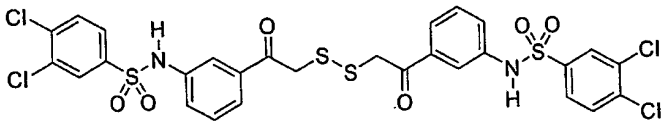


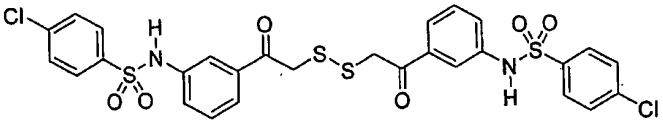


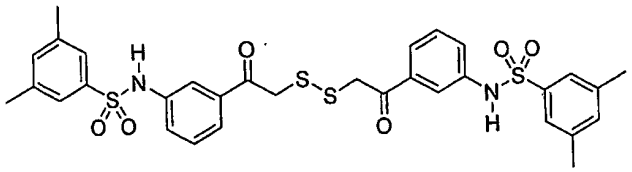




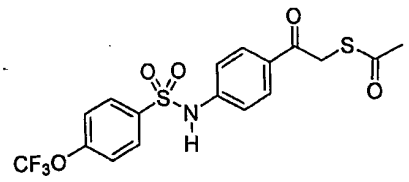


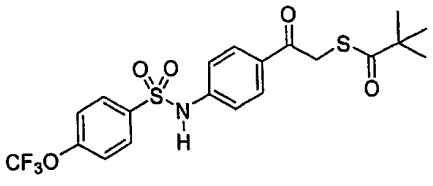


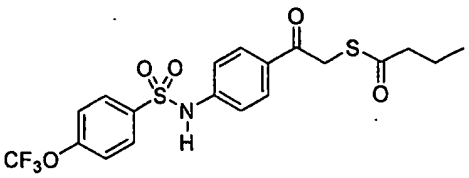


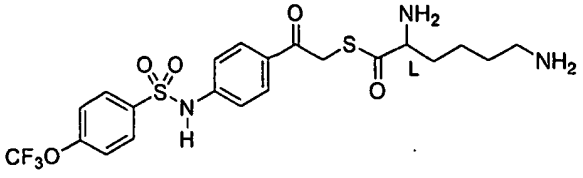


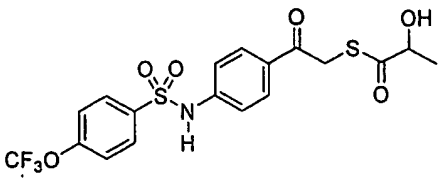
[00155] Preferred thioesters of the invention include compounds of structures I, II, and IV wherein thioester hydrolysis yields an organic acid which is pharmaceutically acceptable including, but not limited to the following exemplary thioesters:

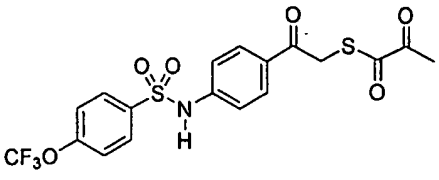


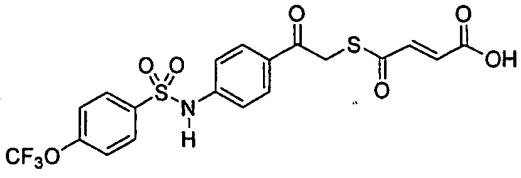


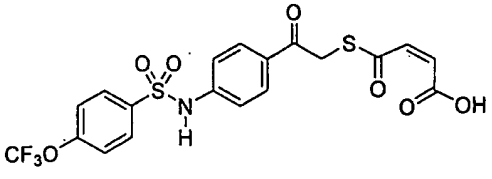


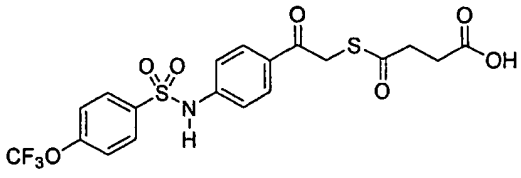


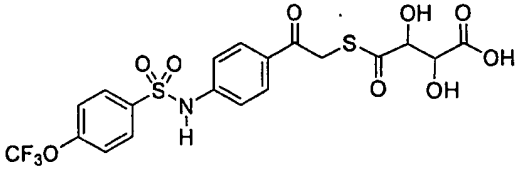


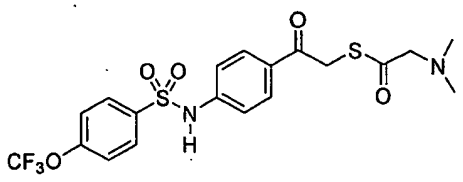


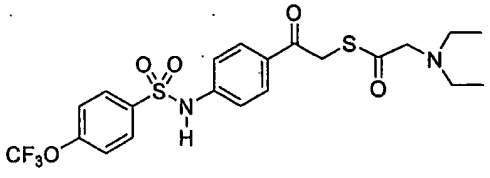


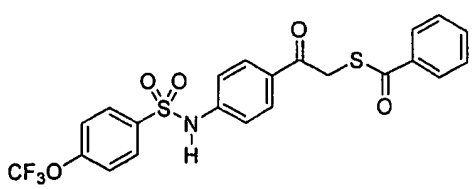


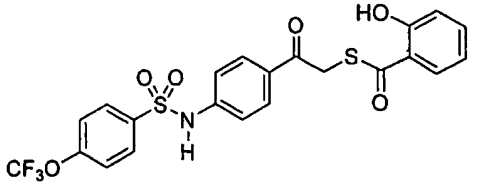


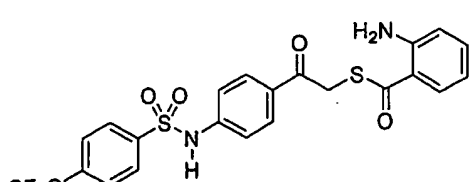


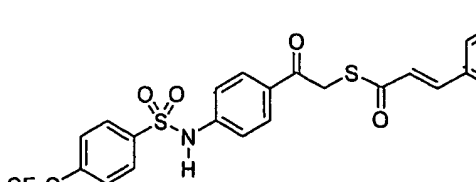


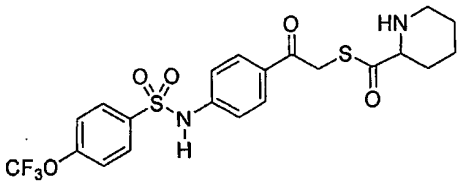


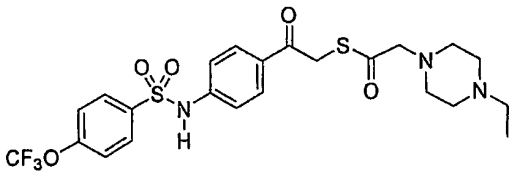


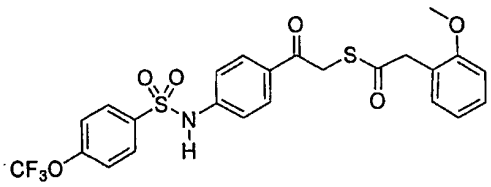


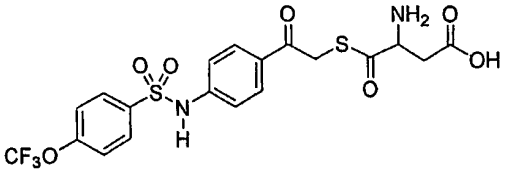


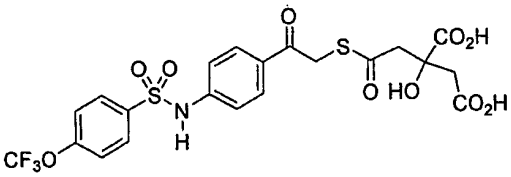


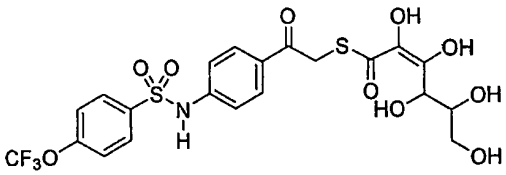


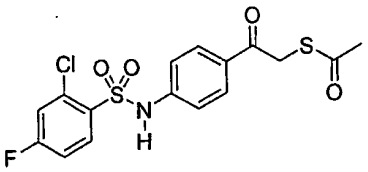


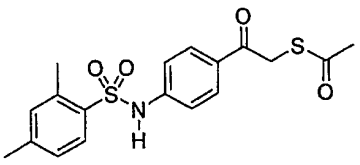


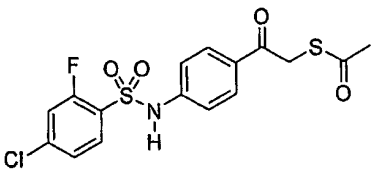


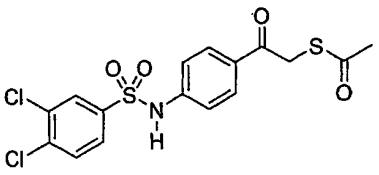


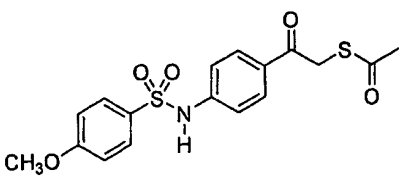


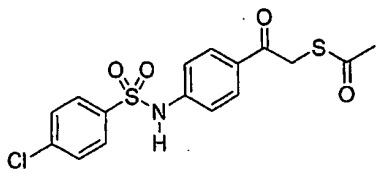


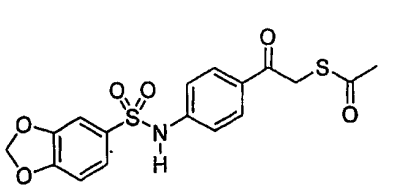


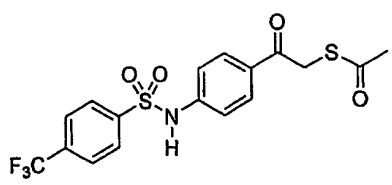


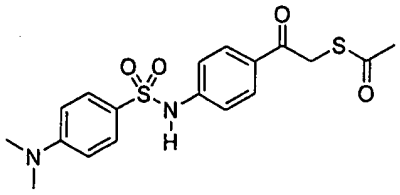


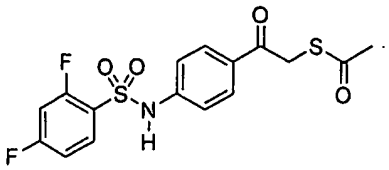


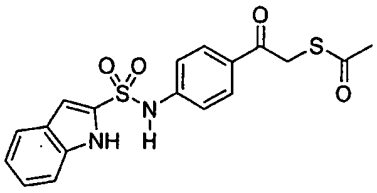


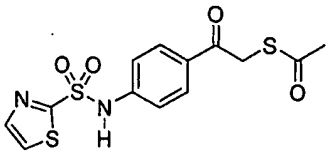


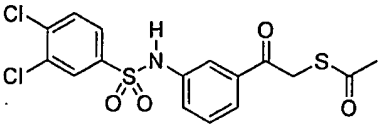


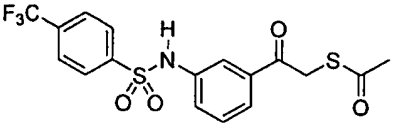


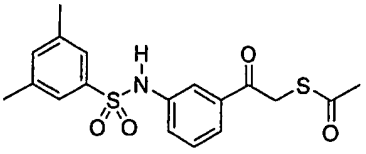






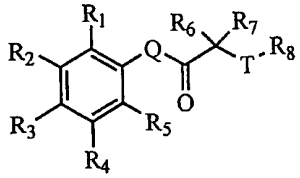






WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, diluent or excipient and a compund having structural formula I,

(I) 

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,

wherein

a) R_1-R_5 is each independently selected from the group consisting of

i) hydrogen;

ii) lower alkyl;

iii) halogen or perhaloalkyl;

iv) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2 or 3; and

v) a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, aryl, lower perfluoroalkyl, and heteroaryl; and

n1 is 0, 1, 2, or 3;

C) halogen or lower perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0,1, 2, or 3;

G) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, aryl, lower perfluoroalkyl and heteroaryl; and

n6 is 0, 1, 2, or 3; and

H) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, heteroalkyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, heteroalkyl, aryl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

vi) an acyl of formula $-(X_1)_{n1}-C(O)-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, aryl, perfluoroalkyl, heteroaryl, hydroxy, alkoxy, amino, and $-NH-X_3$,

where X_3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, amino, and amide; and

n1 is 0, 1, 2, or 3; and

vii) cyano;

viii) nitro;

ix) an amino of formula $-(X_{15})_{n15}-NX_{16}X_{17}$, where

X_{15} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_{16} and X_{17}, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n15 is 0 or 1;

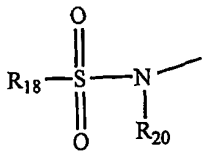
x) a thioether or thiol of formula $-(X_{22})_{n22}-S-X_{23}$, where

X_{22} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{23} is selected from the group consisting of hydrogen, lower alkyl, perflouralkyl aryl, and heteroaryl; and

n22 is 0, 1, 2, or 3;

xi) an N-sulfonamido of structure



wherein

R_{18} is a lower alkyl, lower heteroalkyl, or is a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2, or 3;

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0, or 1;

G) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl, perfluoroalkyl; and

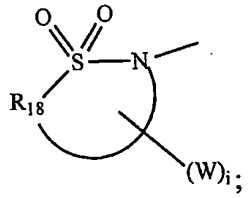
n6 is 0, 1, 2, or 3; and

H) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

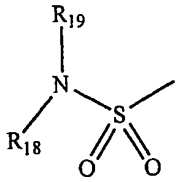
X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, heteroaryl, heteroalkyl, hydroxy, alkoxy, and amide; and
X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, aryl, and heteroaryl, and heteroalkyl;
n7 and n9 are each independently is 0 or 1;

R_{20} is H, lower alkyl, lower aralkyl, or R_{20} taken together with R_{18} forms an optionally substituted five-, six-, seven-, or eight-membered heterocyclic ring, having the following structure:



i is 0, 1, 2, 3, 4;

xii) an S-sulfonamido of formula



wherein R_{18} is a lower alkyl, lower heteroalkyl , or a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, aryl, perhaloalkyl, and heteroaryl; and

n1 is 0, 1, 2 or 3:

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

G) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, aryl, perfluoroalkyl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

H) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

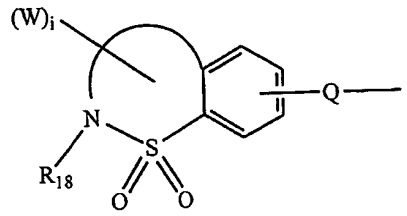
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower heteroalkyl, lower alkenyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower heteroalkyl, lower alkenyl, aryl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

R_{19} is H, C_{1-5} alkyl, C_{1-5} aralkyl, or taken together with one of R_1, R_2, R_3, R_4, or R_5, said R_{19} forms an optionally substituted five-, six-, seven-, or eight-membered heterocyclic ring, having the following structure:



wherein i is 0, 1, 2, 3, 4;

or R_1 and R_2, taken together along with the two ring carbons to which they are attached, or R_2 and R_3, taken together along with the two ring carbons to which they are attached, or R_3 and R_4, taken together along with the two ring carbons to which they are attached, or R_4 and R_5, taken together along with the two ring carbons to which they are attached, form a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a six-membered aromatic or heteroaromatic, or a five- or six-membered heteroaromatic ring, each of which is optionally substituted with one or more substituents, W;

wherein each W is independently selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) optionally substituted aryl;

iv) optionally substituted heterocyclyl;

v) an alkoxy of formula $-(X_{13})_{n13}-O-X_{14}$, where

X_{13} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{14} is selected from the group consisting of hydrogen, lower alkyl, perhaloalkyl, aryl, and heteroaryl; and

n13 is 0, 1, 2, or 3;

vi) halogen or perhaloalkyl;

vii) cyano;

viii) nitro;

ix) an amino of formula $-(X_{15})_{n15}-NX_{16}X_{17}$, where

X_{15} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_{16} and X_{17}, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n15 is 0, 1, 2, or 3; and

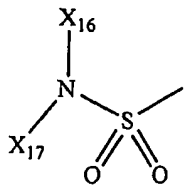
x) a thioether or thiol of formula $-(X_{22})_{n22}-S-X_{23}$, where

X_{22} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{23} is selected from the group consisting of hydrogen, lower alkyl, perfluoroalkyl, aryl, and heteroaryl; and

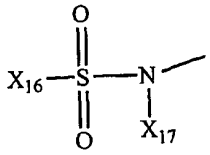
n22 is 0, 1, 2, or 3;

xi) an S-sulfonamido of formula



wherein X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, lower heteroalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

xii) an N-sulfonamido of structure



wherein X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, lower heteroalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

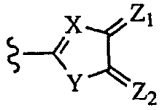
b) R_6 and R_7 are each independently selected from the group consisting of hydrogen and lower alkyl;

c) R_8 is selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) cyano;

iv) 

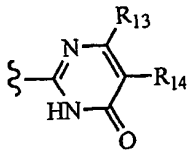
wherein

X is selected from CH and nitrogen;

Y is selected from the group consisting of CH_2, NH, oxygen and sulfur;

Z_1 and Z_2 are each independently selected from the group consisting of null, oxygen, sulfur, and $CR_{11}R_{12}$,

wherein R_{11} and R_{12} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy; and

v) 

wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy;

vi) optionally substituted acyl of the formula $-C(O)R_E$, wherein $HOC(O)R_E$ is any pharmaceutically acceptable acid;

vii) or R_8 is equivalent to the balance of Formula I to form a disulfide dimer;

d) Q is selected from the group consisting of a bond, oxygen, sulfur, $-(CH_2)_m-$, $-(CH_2)_mNH-$, $-(CH_2)_m(CO)-$, $-(CH_2)_mNH(CO)-$, and $-(CH_2)_mC(O)NH-$, wherein m is 0-7, wherein if Q is not symmetric, Q may be attached in either order; and

e) T is selected from the group consisting of oxygen, sulfur, and $-NR_{17}$, wherein R_{17} is selected from the group consisting of hydrogen, lower alkyl, and aryl.

2. The composition of Claim 1, wherein R_1-R_5 are hydrogen.

3. The composition of Claim 1, wherein R_2 is an alkoxy.

4. The composition of Claim 3, wherein said alkoxy is selected from the group consisting of methoxy, ethoxy, propoxy, n-butoxy, t-butoxy, and isobutoxy.

5. The composition of Claim 1, wherein R_3 is an alkoxy.

6. The composition of Claim 5, wherein said alkoxy is selected from the group consisting of methoxy, ethoxy, propoxy, n-butoxy, t-butoxy, and isobutoxy.

7. The composition of Claim 1, wherein R_3 is a halogen.

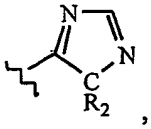
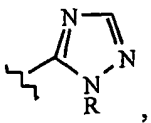
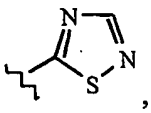
8. The composition of Claim 7, wherein said halogen is chlorine

9. The composition of Claim 7, wherein said halogen is bromine.

10. The composition of Claim 1, wherein R_3 is a perhaloalkyl.

11. The composition of Claim 10, wherein said perhaloalkyl is selected from the group consisting of trifluoromethyl, pentafluoroethyl, and heptafluoropropyl.

12. The composition of Claim 1, wherein R_3 is a heterocyclyl.

13. The composition of Claim 12, wherein said heterocyclyl is selected from the group consisting of furan, thiophene, pyrrole, pyrroline, pyrrolidine, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, triazole, thiadiazole, pyran, pyridine, piperidine, morpholine, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine,  ,  , and  , wherein R is selected from hydrogen and lower alkyl.

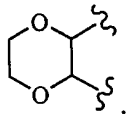
14. The composition of Claim 13, wherein said heterocyclyl is pyrrolidine.

15. The composition of Claim 13, wherein said heterocyclyl is morpholine.

16. The composition of Claim 1, wherein R_3 is -NH(CO)R, wherein R is selected from hydrogen, and lower alkyl.

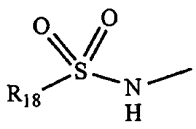
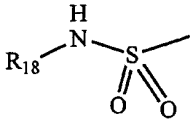
17. The composition of Claim 16, wherein said alkyl is selected from the group consisting of methyl, ethyl, propyl, n-butyl, t-butyl, and isobutyl.

18. The composition of Claim 1, wherein R_2 and R_3, taken together along with the two ring carbons to which they are attached form a six-membered heterocyclic ring.

19. The composition of Claim 18, wherein R_2 and R_3, taken together along with the two ring carbons to which they are attached form  .

20. The composition of Claim 1, wherein R_3 or R_4 is an optionally substituted N-sulfonamido or an optionally substituted S-sulfonamido.

21. The composition of Claim 20 wherein R_3 or R_4 has the structure

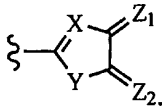
 or 

wherein R_{18} is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl.

22. The composition of Claim 21 wherein R_{18} is phenyl, singly or multiply substituted with C_{1-5} alkyl, C_{1-5} perhaloalkyl, C_{1-5} alkoxy, C_{1-5} perhaloalkyl alkoxy, and N-alkylamido.

23. The composition of Claim 1, wherein R_6 and R_7 are hydrogen.

24. The composition of Claim 1, wherein R_8 is cyano.

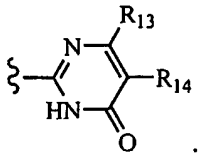
25. The composition of Claim 1, wherein R_8 is  .

26. The composition of Claim 25, wherein X is nitrogen, Y is oxygen and Z_1 and Z_2 are null.

27. The composition of Claim 25, wherein X is nitrogen, Y is NH, Z_1 is oxygen and Z_2 is null.

28. The composition of Claim 25, wherein X is nitrogen, Y is NH, and Z_1 and Z_2 are oxygen.

29. The composition of Claim 24, wherein X is nitrogen, Y is sulfur, Z_1 is (H)(OH) and Z_2 is null.

30. The composition of Claim 1, wherein R_8 is  .

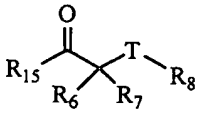
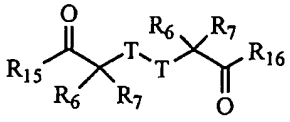
31. The composition of Claim 30, wherein R_{13} and R_{14} are hydrogen.

32. The composition of Claim 30, wherein R_{13} is lower alkyl and R_{14} are hydrogen.

33. The composition of Claim 32, wherein said alkyl is selected from the group consisting of methyl, ethyl, propyl, n-butyl, t-butyl, and isobutyl.

34. The composition of Claim 1, wherein T is sulfur.

35. A pharmaceutical composition comprising a pharameutically acceptable carrier, diluent or excipient and a compound having a structure of Formula II or III,

(II)  (III) 

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,

wherein

a) T is selected from the group consisting of oxygen, sulfur, and $-NR_{17}$, wherein R_{17} is selected from the group consisting of hydrogen, lower alkyl, and aryl;

b) R_{15} and R_{16} are each independently selected from the group consisting of

i) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2, or 3; and

ii) a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

A) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

B) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2 or 3

C) halogen or perhaloalkyl;

D) cyano;

E) nitro;

F) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

G) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, aryl, perhaloalkyl, and heteroaryl; and

n6 is 0, 1, 2 or 3; and

H) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

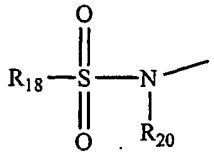
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

I) an N-sulfonamido of structure



wherein

R_{18} is lower alkyl, lower heteroalkyl, or a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

(1) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

(2) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2 or 3;

(3) halogen or perhaloalkyl;

(4) cyano;

(5) nitro;

(6) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and

heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

(7) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, perfluoroalkyl, aryl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

(8) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$ wherein

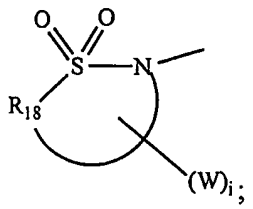
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, and heteroaryl;

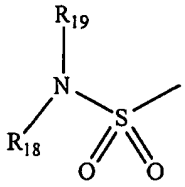
n7 and n9 are each independently is 0 or 1;

R_{20} is H, C_{1-5} alkyl, C_{1-5} aralkyl, or taken together with R_{18} forms an optionally substituted five-, six-, seven-, or eight-membered heterocyclic ring, having the following structure



i is 0, 1, 2, 3, 4;

J) an S-sulfonamido of formula



wherein R_{18} is a lower alkyl, lower heteroalkyl, or a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

(1) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

(2) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2, or 3

(3) halogen or perhaloalkyl;

(4) cyano;

(5) nitro;

(6) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

(7) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_7 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n6 is 0, 1, 2, or 3; and

(8) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

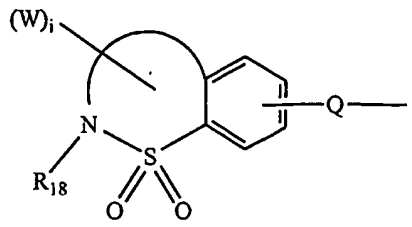
X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and

X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, and heteroaryl;

n7 and n9 are each independently is 0 or 1;

R_{19} is H, C_{1-5} alkyl, C_{1-5} aralkyl, or R_{19} taken together with a portion of the ring to which the S of the S-sulfonamido attaches forms an optionally substituted five-, six-, seven-, or eight-membered heterocyclic ring, having the following structure:



;

W is independently selected from the group consisting of

A) hydrogen;

B) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

C) optionally substituted aryl;

D) optionally substituted heterocyclyl;

E) an alkoxy of formula $-(X_{13})_{n13}-O-X_{14}$, where

X_{13} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{14} is selected from the group consisting of hydrogen, lower alkyl, aryl, lower perhaloalkyl, and heteroaryl; and

i is 0, 1, 2, 3, 4;

iii) an acyl of formula $-(X_1)_{n1}-C(O)-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, aryl, heteroaryl, hydroxy, alkoxy, amino, and $-NH-X_3$,

where X_3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, amino, and amide; and

n1 is 0, 1, 2 or 3; and

iv) cyano;

v) nitro;

vi) an amino of formula $-(X_{15})_{n15}-NX_{16}X_{17}$, where

X_{15} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{16} and X_{17} are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_{16} and X_{17}, taken together with the nitrogen to which they are

attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n15 is 0 or 1; and

vii) a thioether or thiol of formula $-(X_{22})_{n22}-S-X_{23}$, where

X_{22} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{23} is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

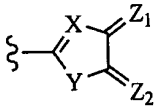
n22 is 0, 1, 2, or 3; and

c) R_8 is selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) cyano;

iv) 

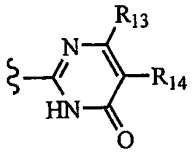
wherein

X is selected from CH and nitrogen;

Y is selected from the group consisting of CH_2, NH, oxygen and sulfur;

Z_1 and Z_2 are each independently selected from the group consisting of null, oxygen, sulfur, and $CR_{11}R_{12}$,

wherein R_{11} and R_{12} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy; and

v) 

wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy;

vi) optionally substituted acyl of the formula $-C(O)R_E$, wherein $HOC(O)R_E$ is any pharmaceutically acceptable acid;

d) R_6 and R_7 are each independently selected from the group consisting of hydrogen and lower alkyl.

36. The composition of Claim 35, wherein R_{15} is an optionally substituted five-, six-, seven-, or eight-membered carbocyclic or an optionally substituted heterocyclic aliphatic ring, or an optionally substituted five-membered or six-membered heteroaryl ring or an optionally substituted six-membered aryl ring.

37. The composition of Claim 35, wherein T is sulfur.

38. The composition of Claim 36, wherein T is sulfur.

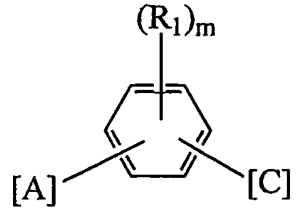
39. The composition of Claim 36, wherein R_{15} is an optionally substituted phenyl.

40. The composition of Claim 39, wherein the phenyl is further substituted with optionally substituted N-sulfonamido or optionally substituted S-sulfonamido.

41. The composition of claim 40 wherein said N-sulfonamido or S-sulfonamido is further substituted with an optionally substituted aryl.

42. The composition of claim 41 wherein said aryl is singly or multiply substituted with C_{1-5} alkyl, C_{1-5} perhaloalkyl, C_{1-5} alkoxy, C_{1-5} perhaloalkyl alkoxy, and N-alkylamido.

43. A compound of Formula IV,

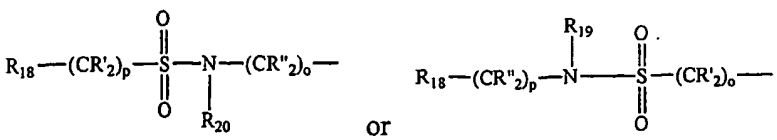


(IV)

or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof,

wherein

a) [A] is



wherein o and p are each independently 0, 1, 2, or 3;

R' and R" are each independently selected from the group consisting of hydrogen and lower alkyl;

R_{18} is a lower alkyl, a lower heteroalkyl, or a five-, six-, seven-, or eight-membered carbocyclic or heterocyclic aliphatic ring, or a five-membered or six-membered heteroaryl ring or a six-membered aryl ring, each optionally substituted with one or more substituents selected from the group consisting of

i) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

ii) an alkoxy of formula $-(X_1)_{n1}-O-X_2$, where

X_1 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_2 is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; and

n1 is 0, 1, 2 or 3;

iii) halogen, partially halogenated alkyl, or perhaloalkyl;

iv) cyano;

v) nitro;

vi) an amino of formula $-(X_3)_{n3}-NX_4X_5$, where

X_3 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_4 and X_5 are each independently selected from the group consisting of hydrogen, lower alkyl, aryl, and heteroaryl; or X_4 and X_5, taken together with the nitrogen to which they are attached, form a five-membered or six-membered heteroaromatic or heteroaliphatic ring; and

n3 is 0 or 1;

vii) a thioether or thiol of formula $-(X_6)_{n6}-S-X_7$, where

X_6 is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

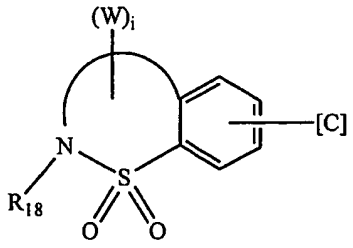
X_7 is selected from the group consisting of hydrogen, lower alkyl, perfluoroalkyl, aryl, and heteroaryl; and
n6 is 0, 1, 2, or 3; and

viii) an amide of formula $-(X_7)_{n7}-NH-C(O)-X_8$ or $-(X_9)_{n9}-C(O)-NH-X_{10}$

X_7 and X_9 are each independently selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_8 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, heteroaryl, hydroxy, alkoxy, and amide; and
X_{10} is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower heteroalkyl, aryl, and heteroaryl;
n7 and n9 are each independently is 0 or 1;

R_{19} is H, C_{1-5} alkyl, or R_{19} taken together with R_1 forms a five-, six-, seven-, or eight-membered heterocyclic ring, and o is 0, and the compound of formula IV has the following structure:



W is independently selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) optionally substituted aryl;

iv) optionally substituted heterocyclyl;

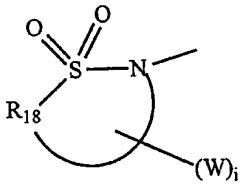
v) an alkoxy of formula $-(X_{13})_{n13}-O-X_{14}$, where

X_{13} is selected from the group consisting of lower alkylene, lower alkenylene, lower alkynylene, aryl, and heteroaryl;

X_{14} is selected from the group consisting of hydrogen, lower alkyl, lower perhaloalkyl, aryl, and heteroaryl; n_{13} = 0, 1, 2, or 3; and

wherein i is 0, 1, 2, 3;

R_{20} is H, C_{1-5} alkyl, or R_{20} taken together with R_{18} forms a five-, six-, seven-, or eight-membered heterocyclic ring, having the following structure:



b) wherein each R_1 is each independently selected from the group consisting of

i) hydrogen;

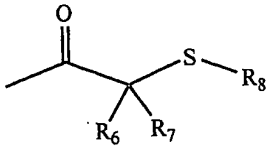
ii) lower alkyl;

iii) lower alkylene;

iv) halogen, partially halogenated alkyl, or perhaloalkyl;

v) an alkoxy or perhaloalkoxy;

c) wherein [C] is



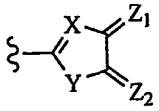
;

d) wherein R_8 is selected from the group consisting of

i) hydrogen;

ii) optionally substituted C_1-C_8 straight-chain, branched, or cyclic saturated or unsaturated alkyl;

iii) cyano;

iv) 

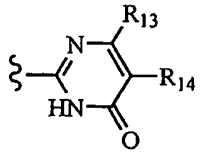
wherein

X is selected from CH and nitrogen;

Y is selected from the group consisting of CH_2, NH, oxygen and sulfur;

Z_1 and Z_2 are each independently selected from the group consisting of null, oxygen, sulfur, and $CR_{11}R_{12}$,

wherein R_{11} and R_{12} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy; and

v) 

wherein R_{13} and R_{14} are each independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, aryl, aryloxy, NH_2, halogen, perhaloalkyl, and hydroxy;

vi) optionally substituted acyl of the formula $-C(O)R_E$, wherein $HOC(O)R_E$ is any pharmaceutically acceptable acid;

vii) or R_8 is equivalent to the balance of Formula IV to form a disulfide dimer; and

e) wherein R_6 and R_7 are each independently selected from the group consisting of hydrogen and lower alkyl.

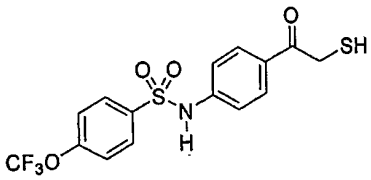
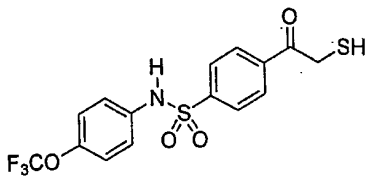
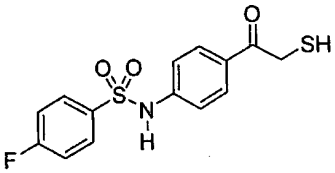
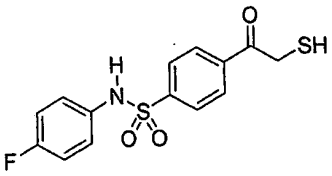
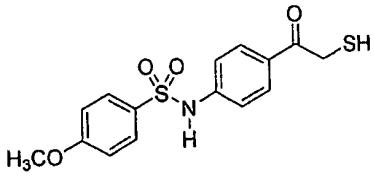
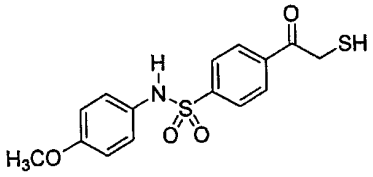
44. The compound of claim 43 wherein R_{19} and R_{20} are each independently H or C_{1-5} alkyl, and o and p are 0.

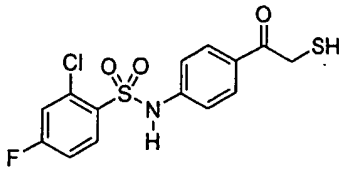
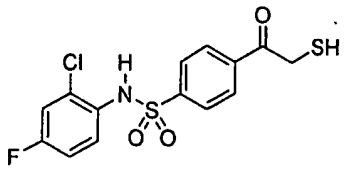
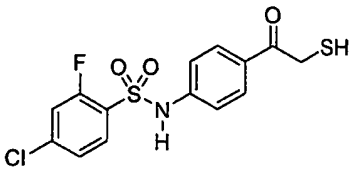
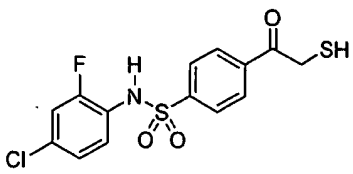
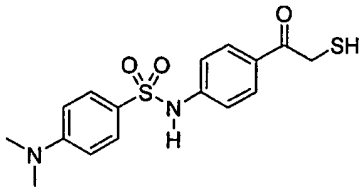
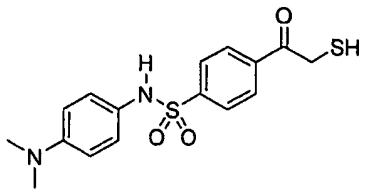
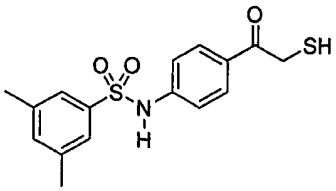
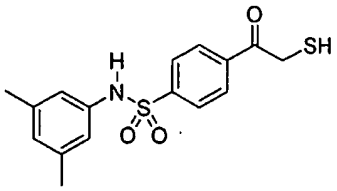
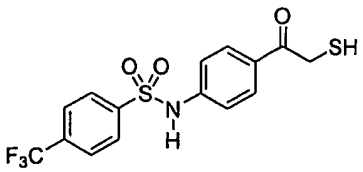
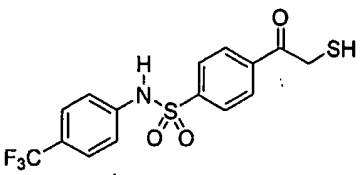
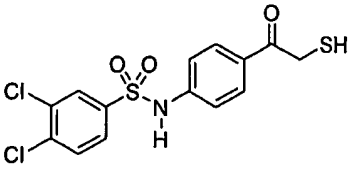
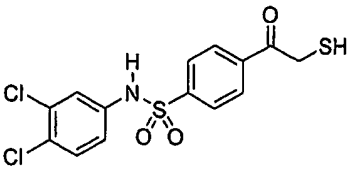
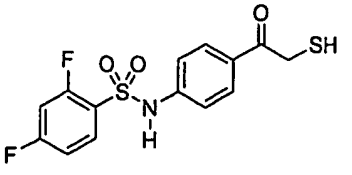
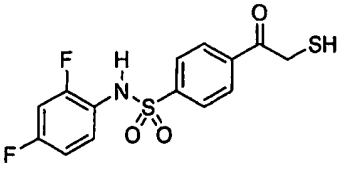
45. The compound of Claim 43, wherein R_{18} is optionally substituted phenyl.

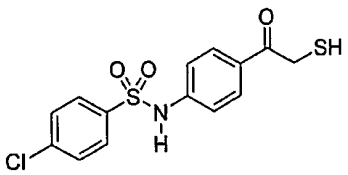
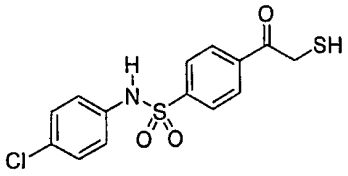
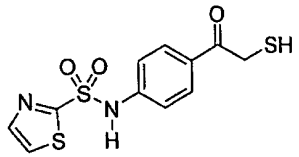
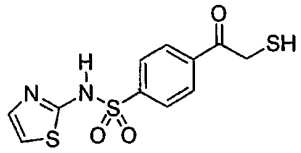
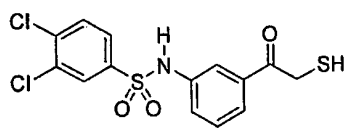
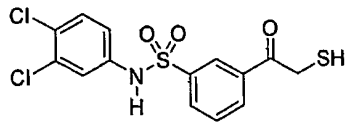
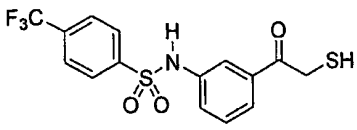
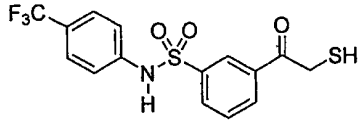
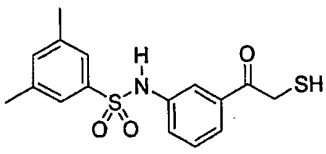
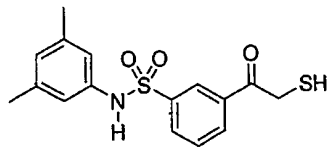
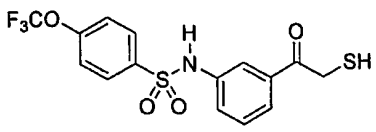
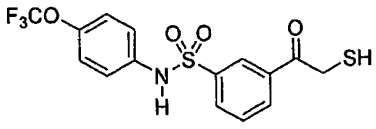
46. The compound of Claim 43 wherein said R_8 is optionally substituted acyl which forms the pharmaceutically acceptable acid $HOC(O)R_E$ upon thioester hydrolysis.

47. The compound of Claim 46 wherein said pharmaceutically acceptable acid HO $C(O)R_E$ is selected from the group consisting of N,N-diethylglycine; 4-ethylpiperazinoacetic acid; ethyl 2-methoxy-2-phenylacetic acid; N,N-dimethylglycine; (nitrophenoxysulfonyl)benzoic acid, acetic acid, maleic acid, fumaric acid, benzoic acid, tartraric acid, glutamic acid, aspartic acid, proline, D-amino acids, butyric acid, palmitic acid, stearic acid, oleaic acid, pipecolic acid, phosphonic acid, phosphoric acid, pivalate (trimethylacetic acid), succinic acid, cinnamic acid, anthranilic acid, salicylic acid, lactic acid, and, pyruvic acids.

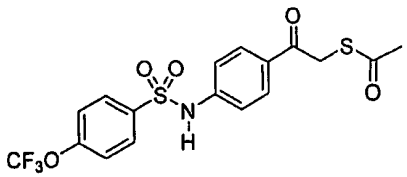
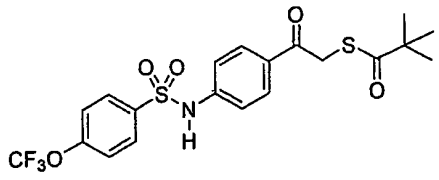
48. The compound of claim 43 wherein R_8 is H and the compound is selected from the group of compounds consisting of

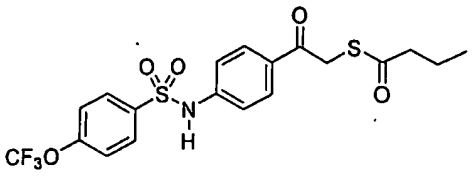







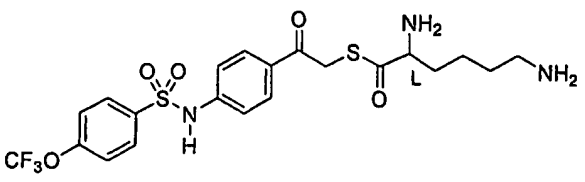















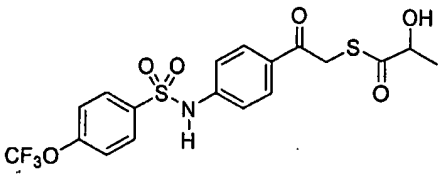













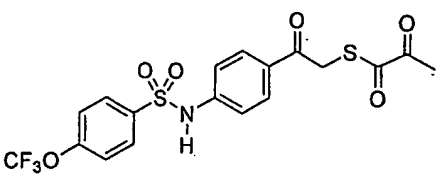
49. The compound of claim 43 wherein R_8 is an optionally substituted acyl and the compound has a structure selected from the group consisting of

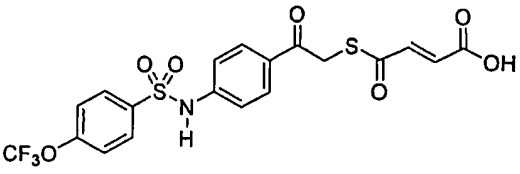



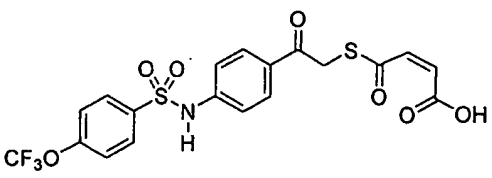


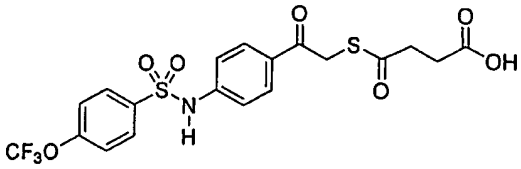


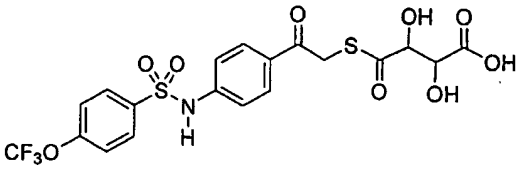


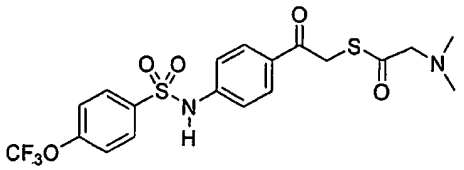


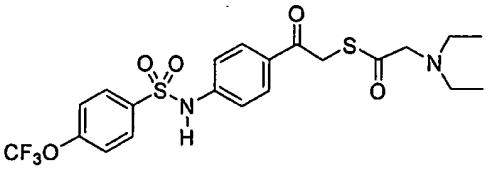


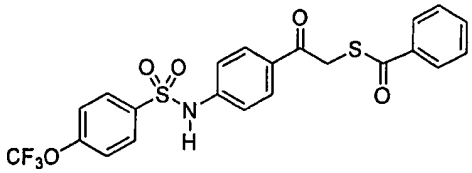


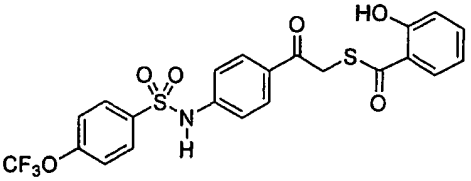


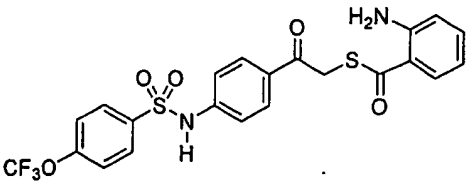


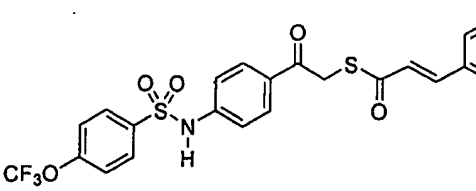


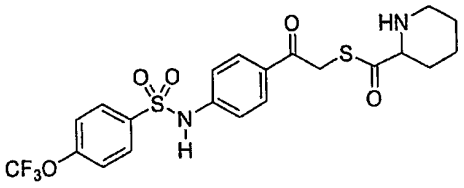


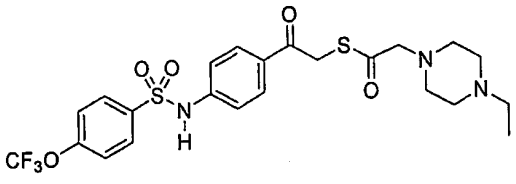


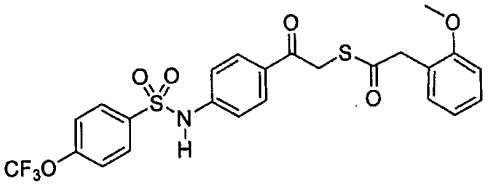


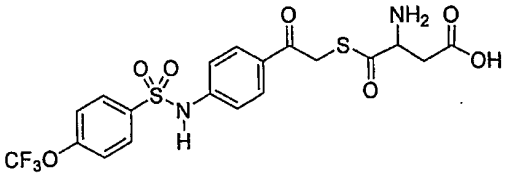


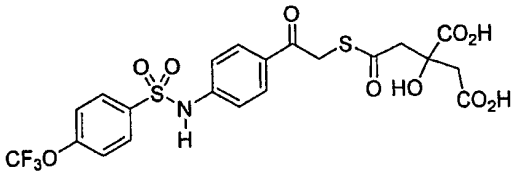


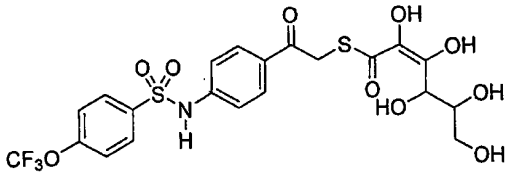


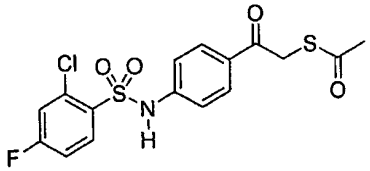


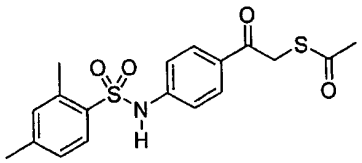


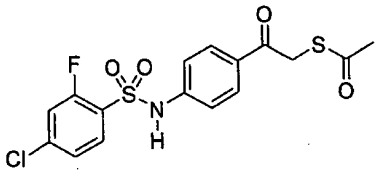


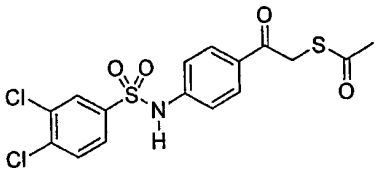


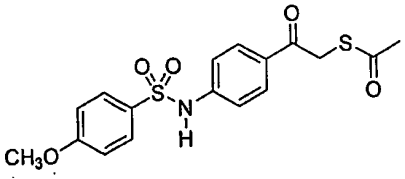


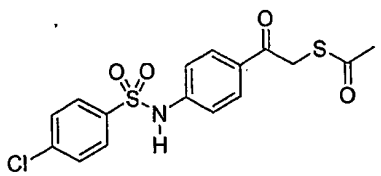


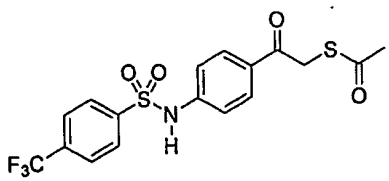


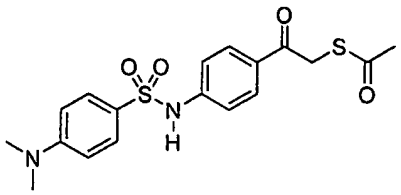


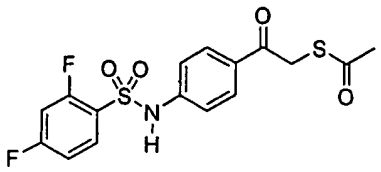


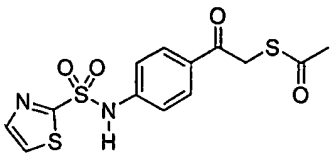


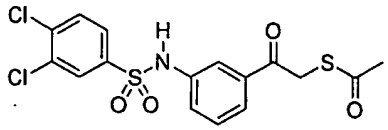


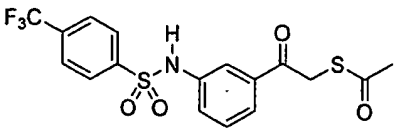


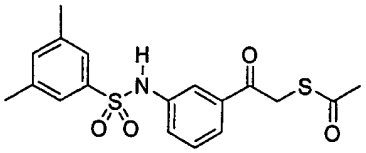




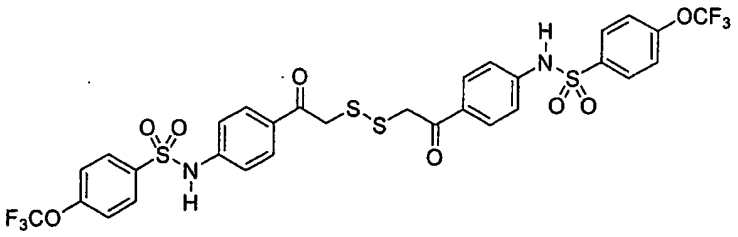


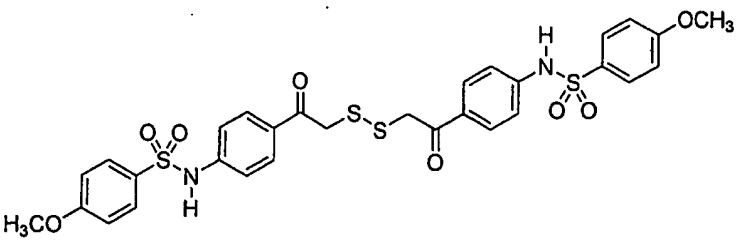


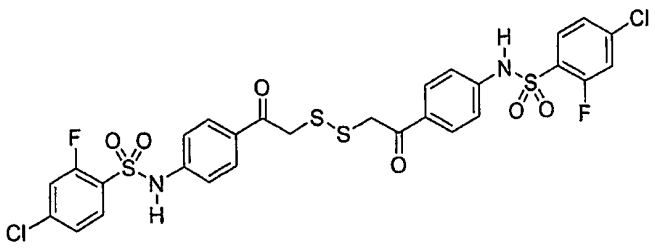


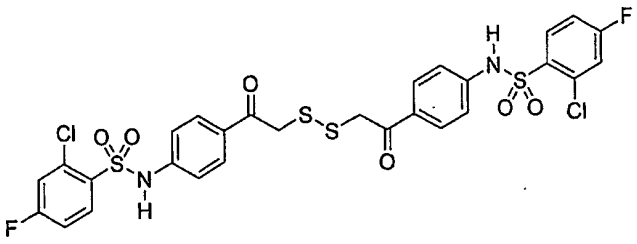


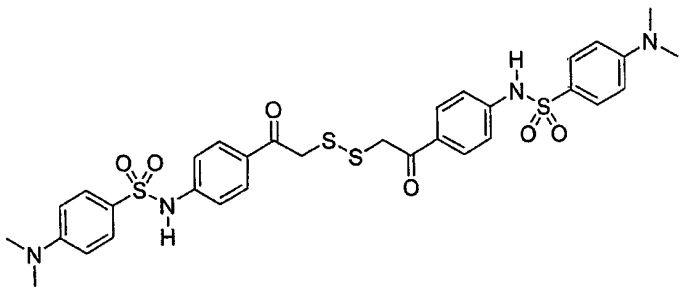
50. The compound of claim 43 wherein R_8 is equivalent to the balance of structure IV so as to form a disulfide dimer and the compound has a structure selected from the group consisting of

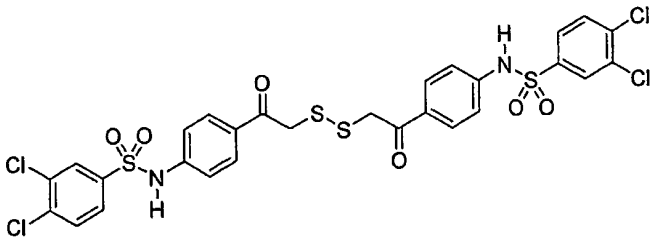


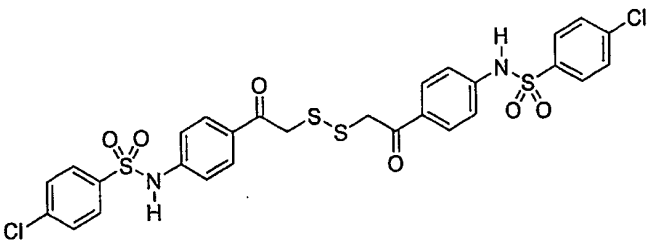


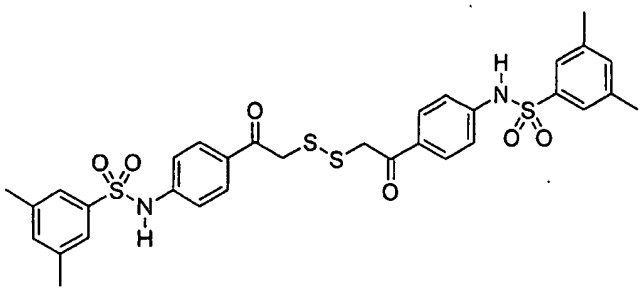


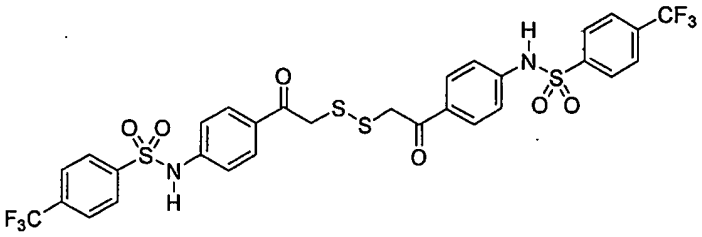


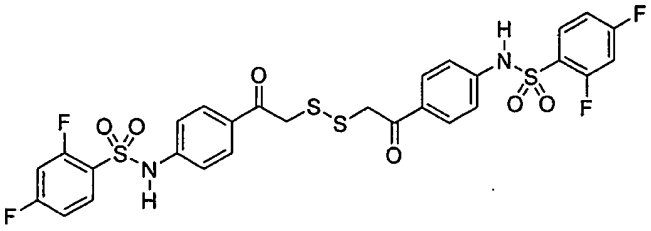


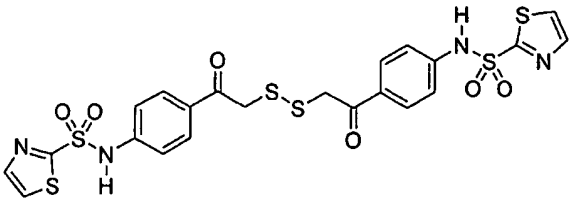


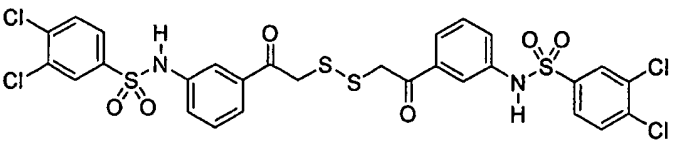


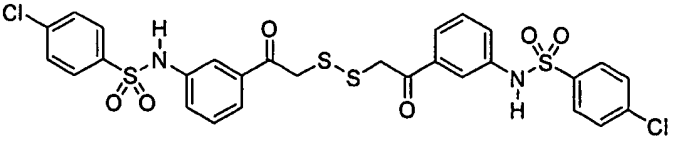


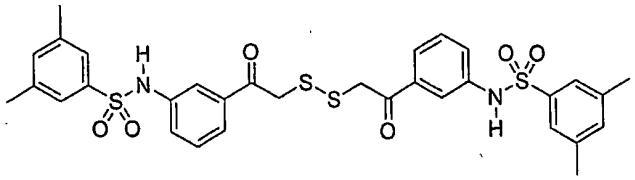




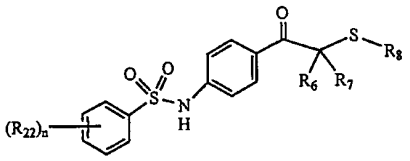




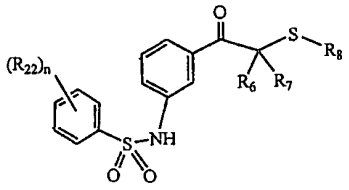




51. A compound having structure of Formula V or VI, VII, or VIII:



(V)



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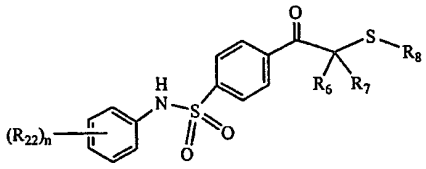
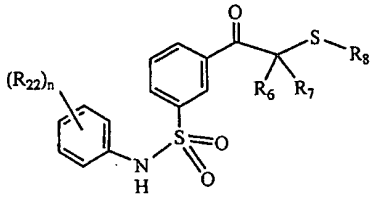


(VII)



(VIII)

or a pharmaceutically acceptable salt amide, ester or prodrug thereof

wherein

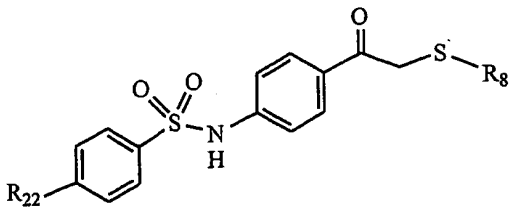
a) R_6 and R_7 are each independently selected from the group consisting of hydrogen and lower alkyl;

b) R_8 is selected from the group consisting of H, acyl, and heterocyclyl, or R_8 is equivalent to the balance of the compound so as to form a disulfide;

c) R_{22} is selected from the group consisting of $C_{1\text{-}5}$ alkyl, $C_{1\text{-}5}$ perhaloalkyl, $C_{1\text{-}5}$ alkoxy, $C_{1\text{-}5}$ perhaloalkyl alkoxy, $C_{1\text{-}5}$ perhaloalkoxy, and N-alkylamido;

d) n = 0, 1, 2, 3.

52. A compound having structural formula V according to claim 51 wherein said compound has the structural formula:



and wherein R_{22} is lower perfluoroalkoxy and R_8 is a thiol protecting group or R_8 is equivalent to the balance of the compound so as to form a disulfide.

53. The compound according to Claim 52 wherein R_{22} is $-OCF_3$.

54. The compound according to Claim 52 wherein R_8 is acetyl.

55. The compound of Claim 43 wherein said compound of Formula IV or pharmaceutically acceptable salt, amide, ester or prodrug thereof is capable of inhibiting the catalytic activity of histone deacetylase (HDAC).

56. A pharmaceutical composition comprising the compound of claim 43 Formula IV or pharmaceutically acceptable salt, amide, ester or prodrug thereof and a pharmaceutically acceptable carrier, diluent, or excipient.

57. A pharmaceutical composition comprising a compound of claim 51 Formula IV or pharmaceutically acceptable salt, amide, ester or prodrug thereof and a pharmaceutically acceptable carrier, diluent, or excipient.

58. The compound of claim 51 wherein said compound of Formula V, VI, VII, or VIII or pharmaceutically acceptable salt, amide, ester or prodrug thereof is capable of inhibiting the catalytic activity of histone deacetylase (HDAC).

59. The pharmacuetical compisition of claim 1 wherein said compound of Formula I, or pharmaceutically acceptable salt, amide, ester or prodrug thereof is capable of inhibiting the catalytic activity of histone deacetylase (HDAC).

60. The pharmacuetical composition of claim 35 wherein said compound of Formula II and III or pharmaceutically acceptable salt, amide, ester or prodrug thereof is capable of inhibiting the catalytic activity of histone deacetylase (HDAC).

61. A method of modulating the catalytic activity of HDAC comprising contacting said HDAC with a pharmaceutical composition of any one of Claims 1, 35, 56, and 57.

62. A method of identifying a carbonyl compound that modulates the function of HDAC, comprising the following steps:

a) contacting cells expressing HDAC with a compound or composition of any one of Claims 1, 35, 43 or 51; and

b) monitoring an effect of said compound or composition upon said cells.

63. The method of Claim 62, wherein said effect is selected from the group consisting of a change in cell phenotype, a change in cell proliferation, a change in the catalytic activity of HDAC, and a change in the interaction between HDAC and a binding partner.

64. A method of treating disease in an individual, comprising identifying an individual in need thereof and administering an effective amount of a pharmacuetical composition of any one of Claims 1, 35, 56 or 57 to said individual.

65. The method of Claim 64, wherein said disease is a hyper-proliferative condition of the human or animal body.

66. The method of Claim 65 wherein the hyper-proliferative condition is selected from the group consisting of colon cancer, breast cancer, ovarian cancer, lung cancer and prostate cancer.

67. The method of Claim 65 wherein the hyper-proliferative condition is selected from the group consisting of cancer of the pancreas, cervix uteri, kidney, brain and central nervous system.

68. The method of Claim 65 wherein the hyper-proliferative condition is selected from the group consisting of non-Hodgkin's lymphomas, multiple myeloma and hematopoietic malignancies, leukemias, Chronic Lymphocytic Leukemia, and lymphomas.

69. The method of Claim 64, wherein said disease is selected from the group consisting of a neurological disorder, and polyglutamine-repeat disorders.

70. The method of Claim 69, where the polyglutamine-repeat disorder is selected from the group consisting of Huntington's disease, Spinocerebellar ataxia 1 (SCA 1), Machado-Joseph disease (MJD)/Spinocerebella ataxia 3 (SCA 3), Kennedy disease/Spinal and bulbar muscular atrophy (SBMA) and Dentatorubral pallidolusyian atrophy (DRPLA).

71. The method of Claim 64, wherein said disease is an anemia or thalassemia.

72. The method of Claim 71, wherein the thalassemia is Sickle Cell Disease.

73. The method of Claim 64, wherein said disease is an inflammatory condition.

74. The method of Claim 73, wherein the inflammatory condition is selected from the group consisting of Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD), ulcerative colitis and psoriasis.

75. The method of Claim 64, wherein said disease is an autoimmune disease.

76. The method of Claim 75, wherein the autoimmune disease is selected from the group consisting of Systemic Lupus Erythromatosus (SLE) and Multiple Sclerosis (MS).

77. The method of Claim 64, wherein said disease is a cardiovascular condition.

78. The method of Claim 77, wherein the cardiovascular condition is selected from the group consisting of cardiac hypertrophy and heart failure.

79. Use of a compound or composition according to any one of claims 1, 35, 43 or 51 for the manufacture of a medicament for use in the treatment of a condition mediated by HDAC.

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(54) Title: A USE OF NOVEL 2-OXO-HETEROCYCLIC COMPOUNDS AND THE PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

(57) Abstract: The present invention is related to novel use of 2-oxo-heterocyclic compounds having anticancer activity and the process for preparing them and a pharmaceutical composition comprising the same. The present invention provides a pharmaceutical composition for preventing and treating the cancer disease comprising lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer or cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter, or neoplasms of the central nervous system, therefore, it can be used as the therapeutics for treating and preventing cancer diseases.

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A USE OF NOVEL 2-OXO-HETEROCYCLIC COMPOUNDS AND THE PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

Technical Field

The present invention relates to novel use of 2-oxo-heterocyclic compounds having anticancer activity and the pharmaceutical compositions comprising the same.

Background Art

Cancer is characterized that cell cluster called as tumor caused by abnormal and uncontrolled cell growth, is formed, permeated into neighboring tissue and severe to be transferred to other organ, which is called as neoplasia. Over than 20 million peoples per year are suffered with cancer in the world and among them 6 million people per year were died from the disease. The origin of cancer is classified into internal factor e.g., genetic factor, immunological factor etc and external factor e.g., various chemical substances, radioactive ray, virus etc. Cancer may occur when the balance between oncogene and tumor suppressor genes is collapsed by above explained factors.

Histone is a nuclear protein bound to nucleus DNA and reversible acetylation reaction of histones occurs at ε-amino group of positively charged lysine tail with reversibility. Since the reaction relates to the formation of highly structure of chromatin, it is reported to be correlated with the regulation of the cell cycle and gene expression accompanied with non-histone proteins.

The balance of acetylated status is sustained with the regulation of two enzyme complexes, histone acetyltransferase (HAT) and histone deacetylase (HDAC), and the change of acetylation level is reported to be essential in the change of gene expression. Therefore, the acetylated state of histone can be regulated by compounds inhibiting HDAC activity, according to the structure, for example, (1) butyrate having short chain fatty acid structure (Newmark et al., *Cancer Lett.* 78, pp1-5, 1994), (2) trichostatin A, suberoylanilide hydroxamic acid (SAHA) and oxamflatin having hydroxamic acid structure (Tsuji et al., *J. Antibiot.* (Tokyo) 29, pp1-6, 1976; Richon et al., *Proc. Natl. Acad. Sci.* USA, 95, pp3003-3007, 1998; Kim et al., *Oncogene* 18, pp2461-2470, 1999), (3) cyclic tetrapeptide structure including the 2-amino-8-oxo-9,10-epoxy-decanoyl (AOE); trapoxin A (Kijima et al., J. Biol. Chem. 268, 22429-22435, 1993), (4) cyclic tetrapeptide structure including the AOE; FR901228 and apicidin (Nakjima et al., *Exp. Cell Res.* 241, pp126-33, 1998; Darkin-Rattray et al., *Proc. Natl. Acad. Sci.* USA, 93, pp13143-13147, 1996), (5) benzamide structure; MS-27-275 (Saito et al., *Proc. Natl. Acad. Sci.* USA, 96, pp4592-4597, 1999).

It has been known that these compounds inhibit HDAC enzyme, induce hyper-acetylation of histone protein, cause to hyper-expression of a specific protein family such as tumor inhibiting factor and inhibit the growth of cancer cell resulting in cancer cell death. Accordingly, the compound inhibiting HDAC selectively can be developed to be a promising candidate drug inhibiting cancer cell and inducing to cell death.

However, there has been not reported or disclosed about novel oxopiperidine compound showing potent inhibiting activity of HDAC activity and anticancer activity in any of above cited literatures, the disclosures of which are incorporated herein by reference.

To investigate novel compound having oxopiperidine skeleton showing potent inhibiting activity of HDAC activity and anticancer activity, the inventors of present invention have intensively carried out *in vitro* experiment concerning the inhibition effect on the HDAC enzyme. As a result of the investigation, the inventors finally completed the present invention by confirming that the novel compound of the present invention inhibited HDAC enzyme and it can be useful as an anti-cancer agent.

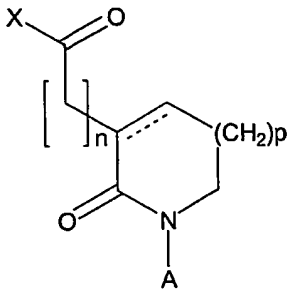
SUMMARY OF THE INVENTION

The present invention also provides a use of novel 2-oxo-heterocyclic compound and the pharmacologically acceptable salt thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases.

The present invention provides a pharmaceutical composition comprising a novel 2-oxo-heterocyclic compound and the pharmacologically acceptable salt thereof as an active ingredient in an effective amount to treat and prevent cancer diseases.

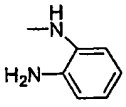
Disclosure of the invention

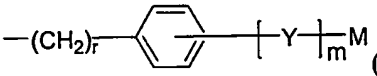
Thus, the present invention provides a novel use of a compound represented by the following general formula (I), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(I)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

A is an hydrogen, A1 group or  (A2),

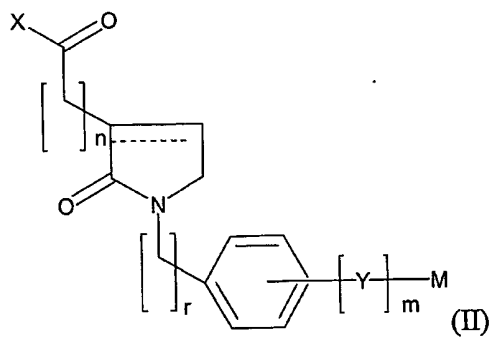
A1 is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group, wherein Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group, M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group, m and r is independently an integer of 1 to 5 respectively in A2 residue;

p is an integer of 0, 1 or 2;

n is an integer of 1 to 5;

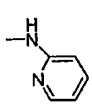
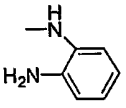
dotted line (⁼) means single bond or double bond.

In preferred embodiment, the present invention also provides a use of the compounds represented by following general formula (II), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(II)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (⎓) means single bond or double bond.

The preferred compound of general formula (II) is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid,

N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide,

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide,

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide,

3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-*m*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

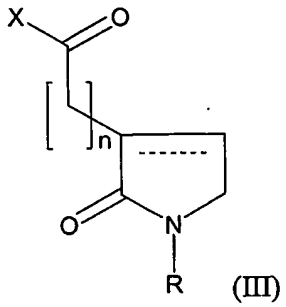
3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

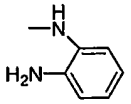
N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

In preferred embodiment, the present invention also provides a use of the compounds represented by following general formula (III), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(III)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

The preferred compound of general formula (III) is one selected from the group consisting of;

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

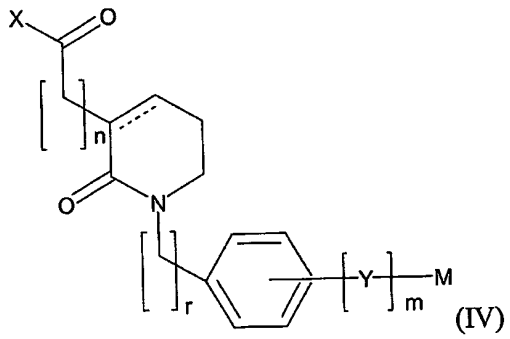
N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

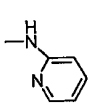
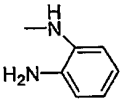
N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

In preferred embodiment, the present invention also provides a use of the compounds represented by following general formula (IV), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(IV)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (⎓) means single bond or double bond.

The preferred compound of general formula (IV) is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetragydropyridin-3-yl]-N-hydroxypropionamide,

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-[2-oxo-1-(4-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide,

N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide,

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid,

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide,

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid,

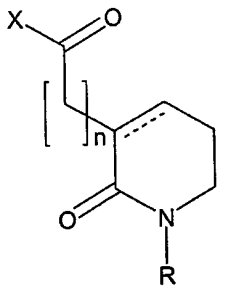
4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide,

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide,

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide,

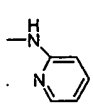
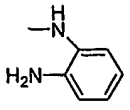
N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide.

In preferred embodiment, the present invention also provides a use of the compounds represented by following general formula (V), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(V)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiophenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

The preferred compound of general formula (V) is one selected from the group consisting of;

3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

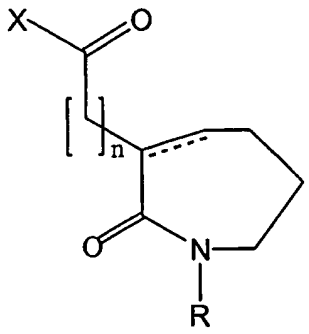
3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-hydroxy-3-(1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

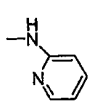
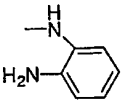
N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide.

In preferred embodiment, the present invention also provides the compounds represented by following general formula (VI), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases and the use thereof:



(VI)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is independently hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C4 carbon atoms substituted with a phenyl group which can be substituted with halogen atom or lower alkyl group;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

The preferred compound of general formula (VI) is one selected from the group consisting of;

N-3-(1-benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-ethyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-butyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide.

It is another object of the present invention to provide the pharmaceutical composition comprising an efficient amount of the compound represented by general formula (I) to (VI) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to prevent or treat cancer diseases together with pharmaceutically acceptable carriers or diluents.

The inventive compounds represented by general formula (I) to (VI) can be transformed into their pharmaceutically acceptable salt and solvates by the conventional method well known in the art. For the salts, acid-addition salt thereof formed by a pharmaceutically acceptable free acid thereof is useful and can be prepared by the conventional method. For example, after dissolving the compound in the excess amount of acid solution, the salts are precipitated by the water-miscible organic solvent such as methanol, ethanol, acetone or acetonitrile to prepare acid addition salt thereof and further the mixture of equivalent amount of compound and diluted acid with water or alcohol such as glycol monomethylether, can be heated and subsequently dried by

evaporation or filtrated under reduced pressure to obtain dried salt form thereof.

As a free acid of above-described method, organic acid or inorganic acid can be used. For example, organic acid such as methansulfonic acid, *p*-toluensulfonic acid, acetic acid, trifluoroacetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonylic acid, vanillic acid, hydroiodic acid and the like, and inorganic acid such as hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, tartaric acid and the like can be used herein.

Further, the pharmaceutically acceptable metal salt form of inventive compounds may be prepared by using base. The alkali metal or alkali-earth metal salt thereof can be prepared by the conventional method, for example, after dissolving the compound in the excess amount of alkali metal hydroxide or alkali-earth metal hydroxide solution, the insoluble salts are filtered and remaining filtrate is subjected to evaporation and drying to obtain the metal salt thereof. As a metal salt of the present invention, sodium, potassium or calcium salt are pharmaceutically suitable and the corresponding silver salt can be prepared by reacting alkali metal salt or alkali-earth metal salt with suitable silver salt such as silver nitrate.

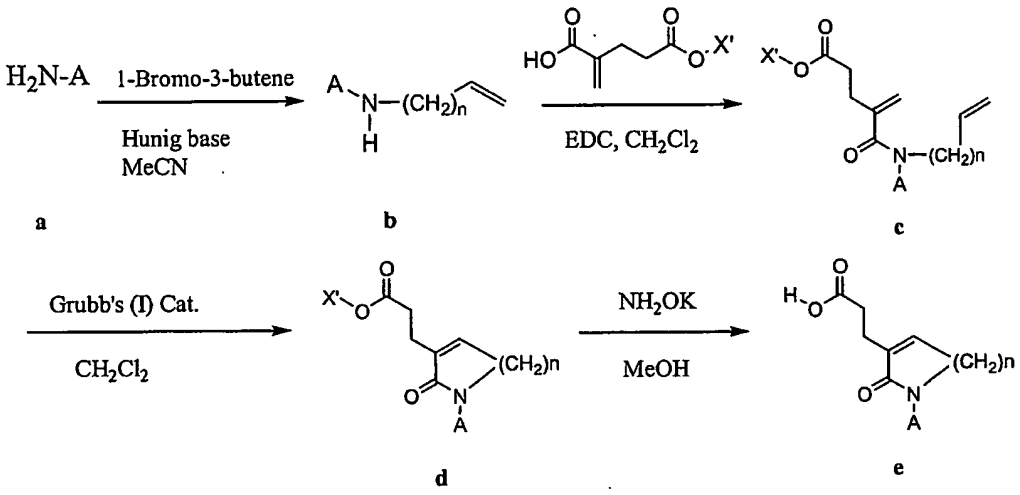
The pharmaceutically acceptable salt of the compound represented by general formula (I) to (VI) comprise all the acidic or basic salt which may be present at the compounds, if it does not indicated specifically herein. For example, the pharmaceutically acceptable salt of the present invention comprise the salt of hydroxyl group such as the sodium, calcium and potassium salt thereof; the salt of amino group such as the hydrogen bromide salt, sulfuric acid salt, hydrogen sulfuric acid salt, phosphate salt, hydrogen phosphate salt, dihydrophosphate salt, acetate salt, succinate salt, citrate salt, tartarate salt, lactate salt, mandelate salt, methanesulfonate(mesylate) salt and *p*-toluenesulfonate (tosylate) salt etc, which can be prepared by the conventional method well known in the art.

There may exist in the form of optically different diastereomers since the compounds represented by general formula (I) to (VI) have unsymmetrical centers, accordingly, the compounds of the present invention comprise all the optically active isomers, R or S stereoisomers and the mixtures thereof. Present invention also comprises all the uses of racemic mixture, more than one optically active isomer or the mixtures thereof as well as all the preparation or isolation method of the diastereomer well known in the art.

The compounds of the invention of formula (I) to (VI) may be chemically synthesized by the methods which will be explained by following reaction schemes hereinafter, which are merely exemplary and in no way limit the invention. The reaction schemes show the steps for preparing the representative compounds of the present invention, and the other compounds also may be produced by following the steps with appropriate modifications of reagents and starting materials, which are envisaged by those skilled in the art.

GENERAL SYNTHETIC PROCEDURES

Scheme 1



As depicted in above Scheme 1, the scheme explains the process for preparing hydroxamine compound (**e**) consisting of 4 steps;

At 1st step, compound (**a**) is reacted with 1-bromo-3-butene under organic solvent in the presence of Hung base to synthesize compound (**b**). In the step, an organic solvent such as acetonitrile, dichloromethane etc are preferable and diethylisopropylamine can be used as a Hung base in the amount of 2 to 3 equivalents to the compound (**a**). It is preferable the reaction is performed at the temperature ranging from 0℃ to R. T.

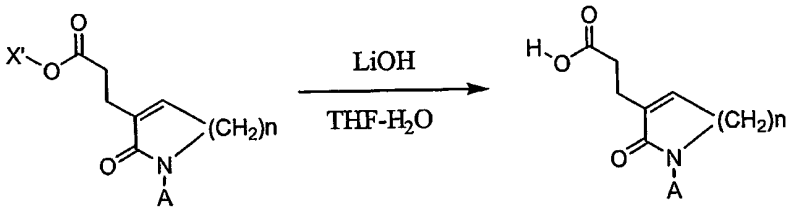
At 2nd step, the compound (**b**) obtained in step 1 is reacted with mono acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide(EDC) under an organic solvent to synthesize the compound (**c**). In the step, an organic solvent such as methylenechloride, THF etc are preferable and a mono acid such as 2-methylene-pentandionic acis-5-methyl ester in the amount of 1 to 1.2 equivalents to the compound (**b**) is preferable. It is preferable the reaction is performed at the temperature ranging from 0℃ to R. T.

At 3rd step, the compound (**c**) obtained in step 2 is converted into the compound (**d**) in the presence of Grubb's (I) catalyst such as Ruthenium catalyst under organic solvent. In the step, it is preferable to use the catalyst in the amount of 0.02 to 0.1 equivalents to the compound (**c**) at the temperature ranging from 0℃ to R. T.

At 4th step, the compound (**d**) obtained in step 3 is reacted with amine salt to synthesize hydroxamide compound (**e**) in case that X is NHOH in general formula I

compounds. In the step, it is preferable to use potassium hydroxamide ($KONH_2$) in the amount of 2 to 3 equivalents to the compound (**d**) at the temperature ranging from 0℃ to R. T.

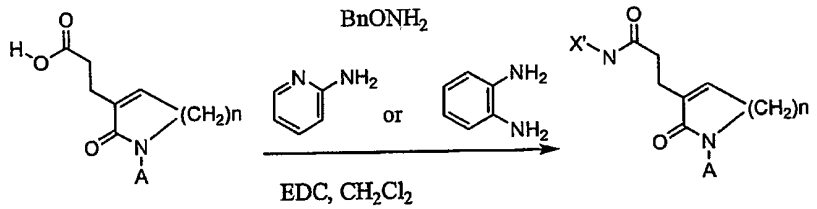
Scheme 2



d **f**

As depicted in the above Scheme 2, the ester compounds (**d**) is reacted with hydroxide metal salt under the organic solvent such as THF to synthesize the carboxylic acid (**f**). In the reaction, it is preferable to use LiOH in the amount of 2 to 3 equivalents to the compound (**d**) at the temperature ranging from 0℃ to R. T.

Scheme 3

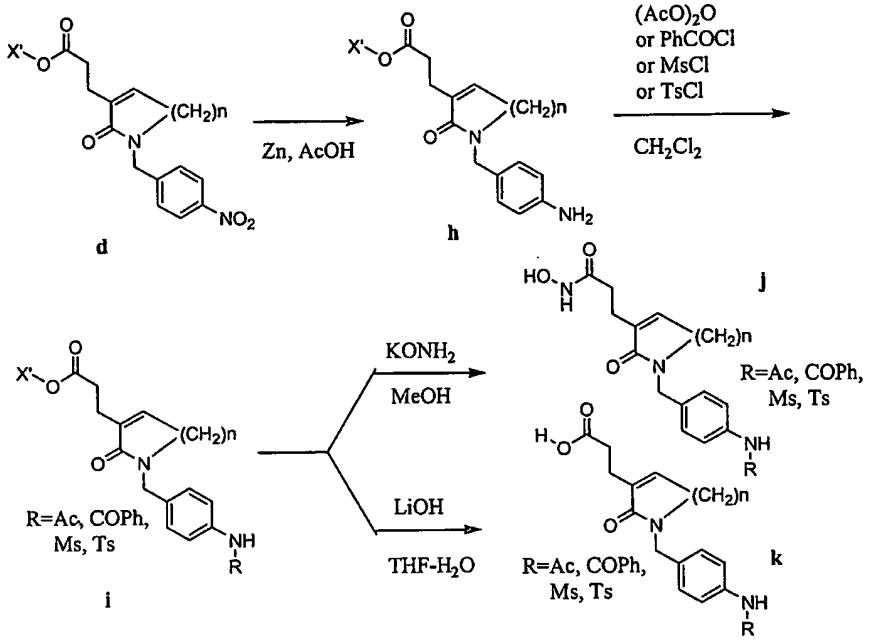


f **g**

As depicted in the above Scheme 3, the carboxylic acid compound (**f**) obtained in Scheme 2 is reacted with benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) under organic solvent to synthesize the amide compounds of which X is benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene group. In the reaction, it is preferable to use benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene in the amount of 1 to 1.5 equivalents to the compound (**f**) at the temperature ranging

from 0℃ to R. T.

Scheme 4



As shown in the above Scheme 4, the amide compound (**j**) and carboxylic acid compound (**k**) are prepared by following procedure from the ester compounds (**d**):

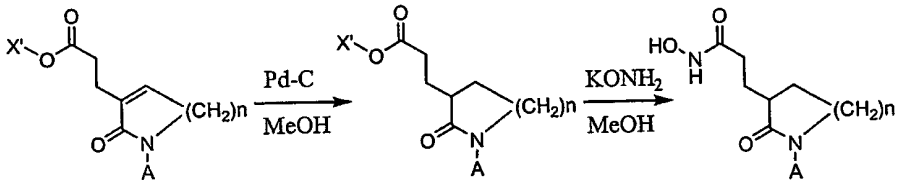
At 1st step, the compound (**d**) prepared from Scheme 2 is reacted with zinc under organic solvent to synthesize the compound (**h**). In the step, it is preferable to use the zinc in the amount of 2 to 5 equivalents of the compound (**h**).

At 2nd step, the compound (**h**) obtained in step 1 is reacted with $(AcO)_2O$, PhCOCl, MsCl or TsCL to synthesize the compound (**i**). In the reaction, it is preferable to use $(AcO)_2O$, PhCOCl, MsCl or TsCL in the amount of 1 to 3 equivalents to the compound (**h**).

At 3rd step, the compound (**i**) obtained in step 2 is reacted with amine salt under the organic solvent such as methanol to produce the hydroxamide compound (**j**), i.e., the general formula I compound wherein X is NHOH where the amine salt is preferably used in the amount of 2 to 3 equivalents to the compound (**i**), or with hydroxide metal salt such as LiOH under the organic solvent such as THF to produce the carboxylic acid compound (**k**), i.e., the general formula I compound wherein X is OH where the metal salt is preferably used in the amount of 2 to 3 equivalents to the

compound (**i**).

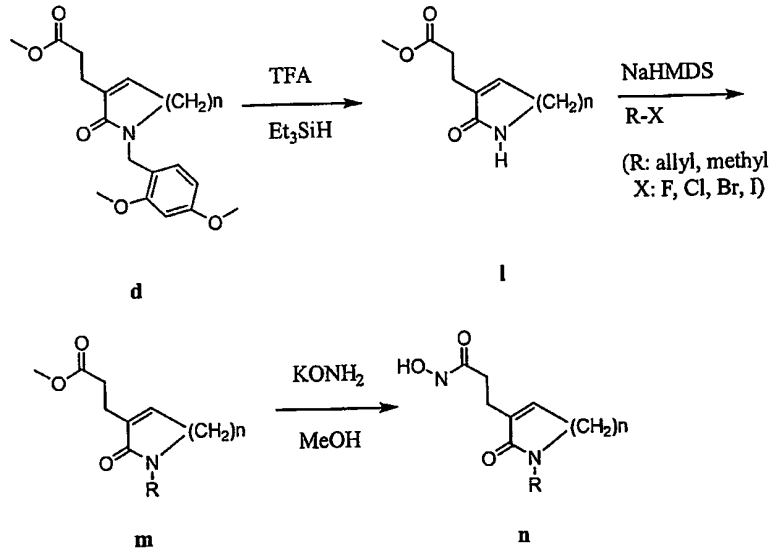
Scheme 5



d **l** **m**

As shown in Scheme 5, the 1,2,5,6-dihydropyridine compound (**d**) is reduced to the piperidine compound (**l**) by reacting with palladium-carbon (Pd/C) under alcohol solvent in the amount of 0.1 to 0.2 equivalents of compound (**d**) and further the piperidine compound (**l**) is reacted with $KONH_2$ under MeOH to synthesize the compound (**m**). In the reaction, it is preferable to use the amine salt in the amount of 2 to 3 equivalents to the compound (**m**) at the temperature ranging from 0℃ to R. T.

Scheme 6

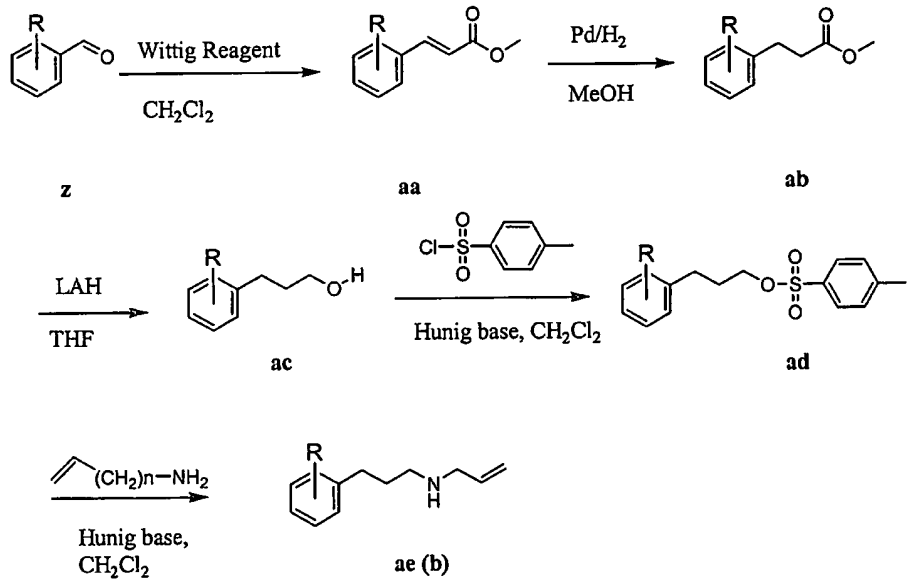


d **l**

m **n**

As shown in Scheme 6, the benzyl compound (**d**) is reacted with triethysilane(TES) in the amount of 1 to 1.5 equivalent of the compound (d) under TFA solution to produce the compound (**l**). The compound (**l**) is further reacted with hexamethyldisilylazidesodium (NaHMDS) under THF solvent and subsequently reacted with R-X (R: ally, methyl etc, X: halogen atom) to produce the compound (**m**). In the reaction, it is preferable to use the NaHMDS in the amount of 1 to 1.5 equivalents to the compound (**l**).

Scheme 7



As shown in Scheme 7, the compound (**b**) as a starting material is prepared by following procedure: At 1st step, the compound (**z**) which can be procure by conventional market or chemical company is reacted with Wittig reagent under the organic solvent such as dichloromethane to synthesize to the compound (**aa**). In the step, it is preferable to use the Wittig reagent in the amount of 1.5 to 2 equivalents of the compound (**z**) at the temperature ranging from 60 to 70℃.

At 2nd step, the compound (**aa**) obtained in step 1 is reacted with Pd/C in the amount of 0.1 to 0.2 equivalents of the compound (**aa**) under ethyl alcohol solvent to synthesize the compound (**ab**).

At 3rd step, the compound (**ab**) obtained in step 2 is reacted with lithium aluminum hydride (LAH) under the organic solvent such as THF to produce the compound (**ac**) at 0 ℃.

At 4th step, the compound (**ac**) substiteis reacted with p-toluenesulfonylchloride, diisopropylethylamine or 4-(dimethylamino) pyridine in the amount of 0.1 to 0.2 equivalents of the compound (**aa**) under ethyl alcohol solvent to synthesize the compound (**ab**).

At 5th step, both of allyl amine and Hunig base, i.e., diisopropylethylamine are added to the compound (**ad**) dissolved in acetonitrile, mixed and stirred for six hours at 80 ℃ to produce the compound (**ae**), one of the compound (**b**).

The present invention also provides a pharmaceutical composition comprising an efficient amount of the compound represented by general formula (I) to (VI) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to treat or prevent cancer diseases together with pharmaceutically acceptable carriers or diluents.

The compound of formula (I) to (VI) according to the present invention can be provided as a pharmaceutical composition containing pharmaceutically acceptable carriers, adjuvants or diluents. For example, the compounds of the present invention can be dissolved in oils, propylene glycol or other solvents which are commonly used to produce an injection. Suitable examples of the carriers include physiological saline, polyethylene glycol, ethanol, vegetable oils, isopropyl myristate, etc., but are not limited to them. For topical administration, the compounds of the present invention can be formulated in the form of ointments and creams.

The pharmaceutical compositions comprising the compound of the present invention can be treat and prevent the cancer disease, for example, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer or cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (eg., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms

of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas).

The compound of the present invention has potent anti-cancer activity, and the pharmaceutical composition of the present invention thus may be employed to treat or prevent the cancer disease.

The present invention also provides a method of preventing or treating the cancer disease which comprises administering compound selected from the group consisting of compounds of formula (I) to (VI) or pharmaceutical acceptable salts thereof in need of such prevention or treatment a therapeutically effective amount of the salt or a pharmaceutically acceptable hydrate thereof as an anti-cancer agent.

Hereinafter, the following formulation methods and excipients are merely exemplary and in no way limit the invention.

The compounds of the present invention in pharmaceutical dosage forms may be used in the form of their pharmaceutically acceptable salts, and also may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

The compounds of the present invention may be formulated into preparations for injections by dissolving, suspending, or emulsifying them in aqueous solvents such as normal saline, 5% Dextrose, or non-aqueous solvent such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol. The formulation may include conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

The desirable dose of the inventive compounds varies depending on the condition and the weight of the subject, severity, drug form, route and period of administration, and may be chosen by those skilled in the art. However, in order to obtain desirable effects, it is generally recommended to administer at the amount ranging 0.0001 - 100 mg/kg, preferably 0.001 – 100 mg/kg by weight/day of the inventive compounds of the present invention. The dose may be administered in single or divided into several times per day. In terms of composition, the compounds should be present between 0.0001 to 10% by weight, preferably 0.0001 to 1% by weight based on the total weight of the composition.

The pharmaceutical composition of present invention can be administered to a subject animal such as mammals (rat, mouse, domestic animals or human) via various routes. All modes of administration are contemplated, for example, administration can be made orally, rectally or by intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular injection.

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

BEST MODE FOR CARRING OUT THE INVENTION

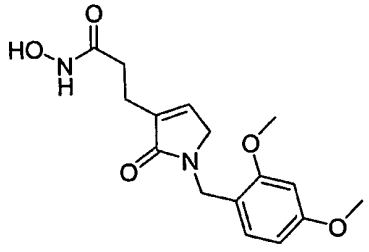
It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, use and preparations of the present invention without departing from the spirit or scope of the invention.

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

EXAMPLES

The following Reference Example, Examples and Experimental Examples are intended to further illustrate the present invention without limiting its scope.

Example 1. Preparation of 3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide(1e)



Step 1. Preparation of allyl-(2,4-dimethoxybenzyl)amine (1b)

0.32ml of allylbromide (3.66mM) and 0.7 ml of diisopropyl ethylamine (3.99 mM) were added to the reaction solution containing 500mg of 2, 4-

dimethoxybenzylamine (3.33 mM) dissolved in methylene chloride with stirring and the solution was left alone at room temperature. After the reaction mixture was neutralized with 10% NaOH solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 276 mg of allyl-(2,4-dimethoxybenzyl)amine (1b) (yield : 40%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J= 8.1 Hz, 1H), 6.44-6.39 (m, 2H), 5.99-5.86 (m, 1H), 5.21-5.09 (m, 2H), 3.79 (d, J= 6.0 Hz, 6H), 3.74 (s, 2H), 3.23 (d, J= 6.0 Hz, 2H)

Step 2. Preparation of 4-[allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-pent-4-enoic acid methyl ester (1c)

253 mg of 2-methylene-pentane dionate-5-methyl ester (1.6 mM), 331mg of [3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.73 mM) and 48mg of 4-(dimethylamino)pyridine (0.39 mM) were added to 0.5 M of reaction solution dissolving the compound (1b) prepared by above step 1 in methylene chloride and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with saturated 10ml of $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 324 mg of 4-[allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-pent-4-enoic acid methyl ester (1c) (yield : 70%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.44 (d, 2H), 5.72 (s, 1H), 5.12 (s, 4H), 4.56-4.81 (m 2H), 3.91-3.83 (m, 2H), 3.78 (d, J= 5.3 Hz, 6H), 3.65 (d, J= 1.4 Hz, 3H), 2.63 (t, J= 5.7 Hz, 2H), 2.54 (t, J= 5.4 Hz, 2H)

Step 3. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (1d)

324mg of the compound (1c) (0.933 mM) prepared by the above Step 2 was added to the catalyst solution containing 74mg of ruthenium (0.09 mM) dissolved in 93ml of CH_2Cl_2. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column

chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 268 mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrole-3-yl]-propionic acid methyl ester (1d) (yield : 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J= 9.0 Hz, 1H), 6.61(br t, 1H), 6.43(s, 1H), 6.40 (d, J= 2.7 Hz, 1H), 4.56 (s, 2H), 3.78(d, J= 5.4 Hz, 9H), 3.65(s, 2H), 2.61(s, 4H)

Step 4. Preparation of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (1e)

100mg of compound (d) prepared by the above Step 3 was dissolved in methanol solution (0.313 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.27 ml, 0.47 mM) was added thereto at 0°C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 50 mg of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (1e) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J= 8.1 Hz,1H), 6.83 (s, 1H), 6.53-6.44 (m, 2H), 4.54(s, 2H), 3.81 (t, J= 2.0 Hz, 6H), 2.56 (t, J= 7.2 Hz, 2H), 2.34 (t, J= 7.4 Hz, 2H), 1.9 (s, 3H)

Example 2. Preparation of 3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (2e)

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (2e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 3. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (3e)

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (3e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 4. Preparation of N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4e)

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 5. Preparation of N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5e)

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 6. Preparation of N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6e)

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 7. Preparation of N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (7e)

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (7e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 8. Preparation of N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8e)

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 9. Preparation of N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (9e)

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (9e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 10. Preparation of N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-

dihydro-1H-pyrrol-3-yl]-propionamide (10e)

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (10e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 11. Preparation of N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (11e)

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (11e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 12. Preparation of 3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (12e)

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (12e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 13. Preparation of 3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (13e)

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (13e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

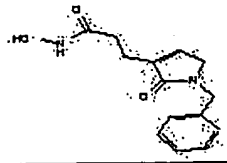
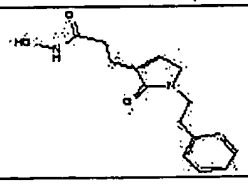
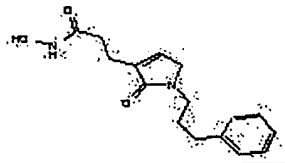
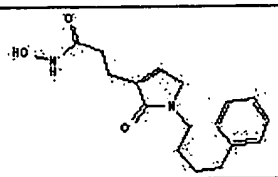
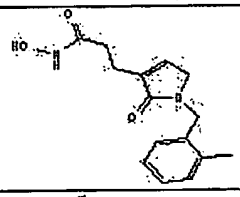
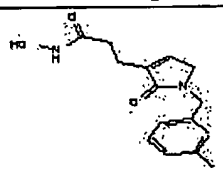
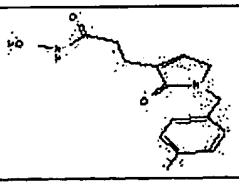
Example 14. Preparation of 3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (14e)

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (14e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

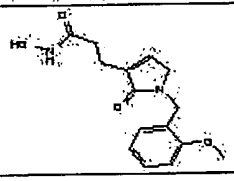
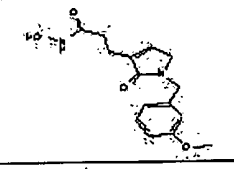
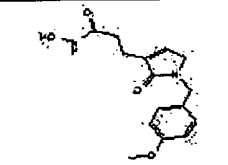
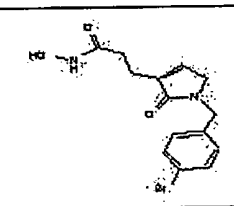
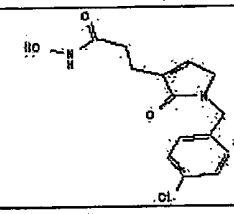
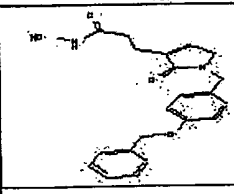
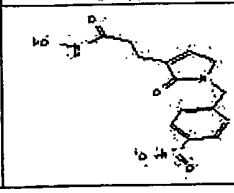
Example 15. Preparation of N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (15e)

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (15e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

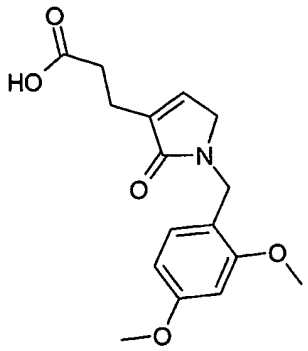
[Table 1a]

Example	Chemical structure	NMR spectrum
2		7.30-7.14 (m, 5H), 6.71 (d, *J*= 18.3 Hz, 1H), 4.59 (d, *J*= 7.8 Hz, 2H), 3.73 (s, 2H), 2.63 (s 4H).
3		7.25-7.09 (m ,5H), 6.64 (s, 1H), 3.62 (t, *J* = 6.1 Hz, 4H), 2.81 (t, *J*= 7.3 Hz, 2H), 2.52 (s, 2H), 2.30 (d, *J*= 6.6 Hz, 2H)
4		7.21 (d, *J*= 7.5 Hz, 2H), 7.12(d, *J*= 6.6 Hz, 3H), 6.72 (s, 1H), 3.75 (s, 2H), 3.41 (s, 2H), 2.57 (d, *J*= 6.3 Hz, 6H), 2.44 (s, 1H), 1.82 (s, 2H)
5		7.28-7.12 (m, 5H), 6.73 (s, 1H), 3.78 (d, *J*= 9.0 Hz, 2H), 3.43 (s, 2H), 2.61 (s, 5H), 1.58 (s, 5H)
6		7.12 (s, 5H), 6.67 (s, 1H), 4.58 (d, *J*= 8.4 Hz, 2H), 3.64 (s, 2H), 2.61 (s, 4H), 2.34-2.22 (m, 3H)
7		7.15 (d, *J*= 6.9 Hz, 1H), 7.02-6.95 (m, 3H), 6.74 (s, 1H), 4.52 (d, *J*= 8.4 Hz, 2H), 3.70 (s, 2H), 2.60 (s, 3H), 2.27 (d, *J*= 4.8 Hz, 4H)
8		7.09-7.03 (m, 4H), 6.70 (d, *J*= 18.3 Hz, 1H), 4.54 (d, *J*= 7.2 Hz, 2H), 3.70 (s, 2H), 2.61 (s, 3H), 2.45 (s, 1H), 2.28 (d, *J*= 13.5 Hz, 3H)

[Table 1b]

Example	Chemical structure	NMR spectrum or LC-MS data
9		7.23-7.18 (m, 1H), 7.08 (d, *J*= 3.5 Hz, 1H), 6.84 (dd, *J*= 5.8 Hz, 2H), 6.72 (s, 1H), 4.59 (s, 2H), 3.78 (s, 3H), 3.75 (s, 2H), 2.60 (s, 2H), 2.44 (s, 2H)
10		7.16 (t, *J*= 4.8 Hz, 1H), 6.73 (t, *J*= 5.4 Hz, 3H), 6.68 (s, 1H), 4.53 (d, *J*= 10.5 Hz, 2H), 3.72 (t, *J*= 5.2 Hz, 5H), 2.59 (s, 2H), 2.43 (s, 2H)
11		7.06-7.014 (m, 4H), 6.71 (s, 1H), 4.49 (s, 2H), 3.66 (s, 2H), 2.59 (s, 2H), 2.43 (s, 2H), 2.25 (s, 3H)
12		7.40 (d, *J*= 7.8 Hz, 2H), 7.05 (d, *J*= 8.4 Hz, 2H), 6.78 (s, 1H), 4.53 (s, 2H), 4.39 (s, 2H), 3.76 (s, 2H), 2.57 (t, *J*= 5.7 Hz, 2H), 2.31 (t, *J*= 7.2 Hz, 2H)
13		7.28-7.07 (m, 2H), 6.95 (t, *J*= 8.2 Hz, 2H), 6.74 (s, 1H), 4.52 (s, 2H), 3.60 (s, 2H), 2.54 (s, 2H), 2.31 (d, *J*= 7.2 Hz, 2H)
14		7.41-7.30 (m,5H), 7.14 (d, *J*= 8.4 Hz, 2H), 6.91 (d, *J*= 8.4 Hz, 2H), 6.67 (s, 1H), 5.02 (s, 2H), 4.55 (s, 2H), 3.72 (s, 2H), 2.65 (2, 4H)
15		RT : 3.82-4.54 (Mass : 306.1)

Example 16. Preparation of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid (16f)



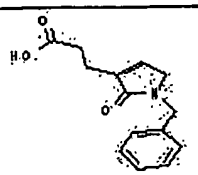
10.8mg of $LiOH \cdot H_2O$ solution (0.25 mM) was added to 0.86ml of THF solution containing 55mg of 3-[1-(2,4-dimethoxy benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.17 mM) in a dropwise manner at 0°C. The reaction mixture was stirred for 2hrs at 0°C adjust pH 1 with 5% HCl was added to the mixture to pH 1. Then the mixture was extracted three times with 10ml of ethyl acetate, the organic layer was washed with 15ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 41 mg of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid (16f) (yield : 80%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J= 9.0 Hz, 1H), 6.65 (br t, 1H), 6.41 (ab,J= 6.5 Hz,1.1 Hz, 2H), 4.57 (s, 2H), 3.81-3.76 (m, 8H), 2.63 (s, 4H)

Example 17. Preparation of 3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid (17f)

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid (17f) was prepared by the similar procedure described in above Example 16 (*See* Table 2).

[Table 2]

Example	Chemical structure	NMR spectrum data
17		7.33-7.19 (m, 5H), 6.69 (br t, 1H), 4.62 (s, 2H), 3.74 (s, 2H), 2.66 (s, 4H)

Example 18. Preparation of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (18j)

Step 1. Preparation of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h)

90mg of 3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.3 mM) was dissolved in methanol solution at room temperature. And then 290mg of Zn (4.44mM) and 0.02ml of acetic acid (0.3 mM) were added thereto and the mixture was stirred for 48 hrs at room temperature. The resulting compound was purified by Silica gel column chromatography with ethylacetate as an eluant to give 20 mg of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h) (yield : 25%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J= 8.4 Hz, 2H), 6.62 (d, J= 1.8Hz, 2H), 6.60 (br t, 1H) 4.48 (s, 2H), 3.68 (d, J= 1.2 Hz, 3H), 3.65 (s, 4H), 2.66-2.58 (m, 4H)

Step 2. Preparation of 3-[1-(4-benzoylamino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (i)

10mg of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h) prepared by above Step 1 was dissolved in methylene chloride solution (0.04mM) at room temperature. And then 8.5 μl of benzoyl chloride (0.07 mM) and 19.1 μl of diisopropylamine (0.11mM) were added thereto and the mixture was stirred for 2 hrs at 0°C. The reaction was stopped by adding methanol and the mixture was extracted three times with 10ml of ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with ethyl acetate and hexane (1:2) as an eluant to give 12 mg of 3-[1-(4-benzoylamino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (i) (yield : 87%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88-7.83 (m, 3H), 7.62-7.47 (m, 6H), 6.68 (br t, 1H), 4.62 (S, 2H), 3.75 (d, 2H), 3.68 (s, 3H), 2.67-2.64 (m, 4H)

Step 3. Preparation of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (j)

7mg of compound (i) prepared by the above Step 2 was dissolved in methanol solution (0.02 mM) and then 1.7 M methanolic suspension solution containing NH_2OK

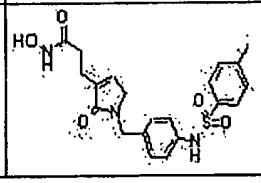
(0.4 ml, 0.68 mM) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.01 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 3.2 mg of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (j) (yield : 46%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J= 6.6 Hz, 2H), 7.62 (d, J= 8.7 Hz, 2H), 7.53-7.39 (m, 4H), 7.17(d, J= 8.4 Hz, 2H), 6.77 (br t, 1H), 4.57 (s, 2H), 3.77 (s, 2H), 2.58 (t, J= 7.3 Hz, 2H), 2.31 (t, J= 7.2Hz, 2H)

Example 19. Preparation of N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (19j)

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (19j) was prepared by the similar procedure described in above Example 18 (*See* Table 3).

[Table 3]

Example	Chemical structure	NMR spectrum data
19		7.61 (t, J= 7.0 Hz, 3H), 7.05-6.89 (m, 6H), 4.54 (s, 3H), 3.74 (s, 3H), 3.39 (s, 3H), 2.37 (s, 3H), RT : 3.87-4.34 (Mass : 430.0)

Example 20. Preparation of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide(20q)

Step 1. Preparation of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o)

587mg of 2-methylene-succinate 4-methyl ester (4.07mM), 781mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (4.07mM) and 75mg of 4-(dimethylamino)pyridine (0.61mM) were added to the reaction solution containing 300mg of allylbenzylamine (2.04 mM) dissolved in methylene chloride solution (0.5M) with stirring for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was diluted with ethyl acetate, washed with

10ml of solution mixture mixed with saturated $NaHCO_3$ solution and saturated NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 272 mg of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o) (yield : 49%).

^{1}H-NMR (300 MHz, CDCl3) δ 7.30-7.22 (m, 5H), 5.84-5.71 (m, 1H), 5.37-5.15 (m, 4H), 4.75-4.65 (m, 2H), 4.02 (s, 2H), 3.63 (s, 3H), 3.48 (s, 2H)

Step 2. Preparation of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p)

234mg of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o) (0.1mM) prepared by the above Step 1 was added to the catalyst solution containing 36mg of Grubb's (I) catalyst (0.04mM) such as ruthenium dissolved in CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 180 mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p) (yield : 85%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 6.94 (t, J= 1.5 Hz, 1H), 4.61 (s, 2H), 3.79(d, J= 0.7 Hz, 2H), 3.70 (s, 3H), 3.37 (d, J= 1.5 Hz, 2H)

Step 3. Preparation of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide (q)

24mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p) prepared by the above Step 2 was dissolved in methanol solution (0.1 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.4 ml, 0.68 mM) was added thereto at 0°C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 12 mg of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide (q) (yield : 48%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 7.05 (br t, 1H), 4.63 (s, 2H), 3.90 (s, 2H), 3.30 (t, J= 1.5 Hz, 1H), 3.13 (s, 2H)

Example 21. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (21q)

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (21q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

Example 22. Preparation of N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide (22q)

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-acetamide (22q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

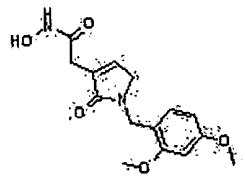
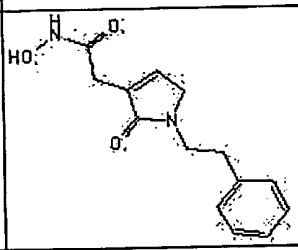
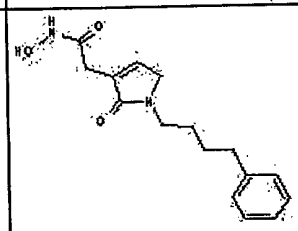
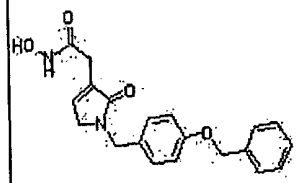
Example 23. Preparation of N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide (23q)

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-acetamide (23q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

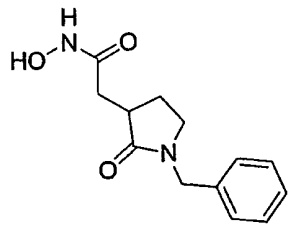
Example 24. Preparation of 2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (24q)

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (24q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

[Table 4]

Example	Chemical structure	NMR spectrum data
21		7.12 (d, J= 8.4 Hz, 2H), 6.90(d, J= 20.7 Hz, 1H), 6.43 (d, J= 6.0 Hz), 4.57 (d, J= 2.7 Hz, 2H), 3.86 (d, J= 15.9 Hz, 2H), 3.79 (d, J= 3.0 Hz, 6H)
22		7.29-7.14 (m, 5H), 6.90 (br t, 1H), 3.75-3.65 (m, 4H), 3.23 (s, 1H), 2.92-2.84 (m, 2H)
23		7.21 (t, J= 7.4 Hz, 2H), 7.11 (d, J= 7.8 Hz,3H), 6.76 (br t, 1H), 5.22 (s, 1H), 3.30 (t, J= 3.3 Hz, 1H), 2.58 (t, J= 7.0 Hz, 2H), 2.04 (s, 3H), 1.82 (s, 3H), 1.57 (s, 4H)
24		7.39-7.31 (m, 5H), 7.13 (d, J= 8.4 Hz, 2H), 6.92 (d, J= 8.7 Hz, 3H), 5.03 (s, 2H), 4.56 (s, 2H), 3.82 (d, J= 13.8 Hz, 2H), 3.53 (s, 1H), 3.31 (s, 1H)

Example 25. Preparation of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s)



Step 1. Preparation of (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r)

30mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester

was dissolved in methanol solution (0.12 mM) under nitrogen atmosphere. Then 2.6mg of Pd-C (0.02mM) was added thereto, and hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with with a solvent mixture mixed with EtOAc and hexane (1:1) as an eluant to give (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r) (yield : 95%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5H), 4.44 (ab, J= 19.8 Hz, 7.4Hz, 2H), 3.67 (s, 3H), 3.21-3.16 (m, 2H), 2.9 6(m, 2H), 2.43 (dd, J= 8.7 Hz, 7.9 Hz, 1H), 2.34-2.23 (m, 1H), 1.76-1.65 (m, 1H)

Step 2. Preparation of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s)

12mg of (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r) prepared by the above Step 1 was dissolved in methanol solution (0.04 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.07 ml, 0.12 mM) was added thereto at 0°C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 1.6 mg of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s) (yield : 8%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5H), 4.46 (d, J= 8.1Hz, 2H), 3.35-3.20 (m, 2H), 3.01-2.71 (m, 2H), 2.66-2.44 (m, 2H), 2.35-2.22 (m, 2H), 1.81-1.58 (m, 2H)

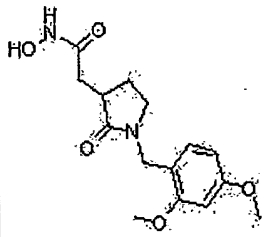
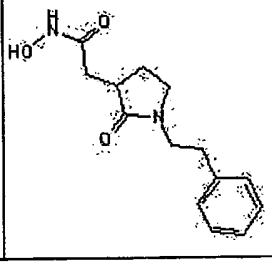
Example 26. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide (26s)

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide (26s) was prepared by the similar procedure described in above Example 25 (*See* Table 5).

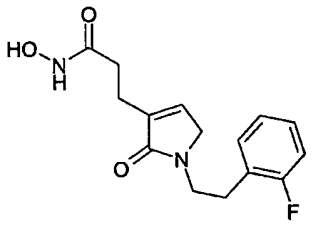
Example 27. Preparation of N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetamide (27s)

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide (27s) was prepared by the similar procedure described in above Example 25 (*See* Table 5).

[Table 5]

Example	Chemical structure	NMR spectrum data
26		7.10 (t, J= 9.3 Hz, 1H), 6.44 (t, J= 2.6 Hz, 2H), 4.43 (dd, J= 14.3 Hz, 14.8 Hz, 2H), 3.78 (s,6H), 3.31-3.21 (m, 2H), 2.88-2.68 (m, 1H), 2.56-2.49 (m, 1H), 2.26-2.22 (m, 1H), 1.71-1.60 (m, 1H)
27		7.30-7.15 (m, 5H), 3.50(t, J= 7.1 Hz, 2H), 3.25-3.11 (m,2H), 2.86-2.66 (m, 3H), 2.57-2.44 (m, 1H), 2.32-2.21 (m, 2H), 1.77-1.62 (m, 1H)

Example 28. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y)



Step 1. Preparation of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u)

1.02g of *p*-toluensulfonyl chloride (5.35mM), 1.24ml of diisopropyl ethylamine (7.13mM) and 86mg of 4-(dimethylamino)pyridine (0.71mM) were added to the reaction solution (3.57mM) containing 500mg of 2-(2-fluoro-phenyl)-ethanol (3.57 mM) dissolved in methylene chloride solution with stirring for 6 hrs at 0 °C under Ar atmosphere, and then the reaction mixture was stirred for 12hrs at room temperature. The resulting mixture was neutralized with ammonium chloride, extracted with ethyl acetate and washed with saturated NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:7) as an

eluant to give 740 mg of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u) (yield : 70%).

Step 2. Preparation of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v)

0.89ml of allylamine (11.89mM) and 0.31ml of diisopropyl ethylamine (1.78mM) were added to the reaction solution (1.19 mM) containing 350mg of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u) prepared by above Step 1 dissolved in acetonitrile solution with stirring for 6 hrs at 80 °C. After the reaction mixture was neutralized with 10% NaOH solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 141 mg of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v) (yield : 66%).

Step 3. Preparation of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w)

106 mg of 2-methylene-pentane dionate-5-methyl ester (0.67 mM), 139mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (0.73 mM) and 20mg of 4-(dimethylamino)pyridine (0.17 mM) were added to reaction solution (0.56mM) dissolving 100mg of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v) prepared by above step 2 in methylene chloride and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with 10ml of saturated $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 128 mg of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w) (yield : 72%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.09 (m, 1H), 7.04-6.94 (m, 3H), 5.84 -5.57 (m, 1H), 5.13 (t, J= 10.7 Hz, 4H), 5.06-4.94 (m, 2H), 3.79 (s, 2H), 3.62 (s, 4H), 3.53 (d, J= 5.4 Hz, 3H), 2.89 (d, J= 6.0 Hz, 3H)

Step 4. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x)

100mg of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w) (0.31mM) prepared by the above Step 3 was added to the catalyst solution containing 27mg of ruthenium catalyst (0.03mM) dissolved in 31.3ml of CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 69 mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x) (yield : 75%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16-7.12 (m, 2H), 7.03-6.93 (m, 2H), 6.59 (br t, 1H), 3.67 -3.65 (m, 4H), 3.62 (s, 3H), 2.89 (t, *J*= 7.3 Hz, 2H), 2.56 (s, 4H)

Step 5. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y)

38mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x) prepared by the above Step 4 was dissolved in methanol solution (0.13 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.38 ml, 0.65 mM) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 25 mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y) (yield : 65%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.08 (m, 2H), 7.02-6.92 (m, 2H), 6.69 (br t, 1H), 3.69 (s, 2H), 3.63 (t, *J*= 7.0 Hz, 2H), 2.87 (t, *J*= 7.0 Hz, 2H), 2.51 (t, *J*= 7.0 Hz, 2H), 2.25 (t, *J*= 7.3 Hz, 2H)

Example 29. Preparation of 3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (29y)

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (29y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 30. Preparation of 3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (30y)

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (30y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 31. Preparation of N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (31y)

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (31y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 32. Preparation of N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (32y)

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (32y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 33. Preparation of N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (33y)

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (33y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 34. Preparation of 3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (34y)

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (34y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 35. Preparation of 3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (35y)

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (35y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 36. Preparation of N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (36y)

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (36y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 37. Preparation of N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (37y)

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (37y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

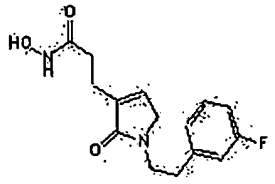
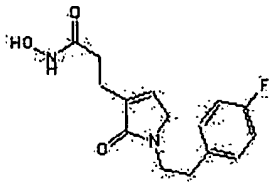
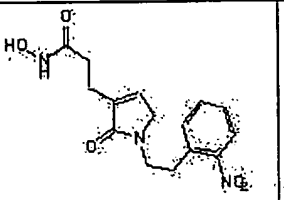
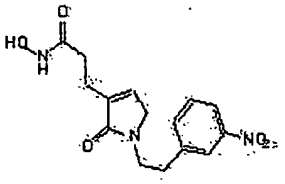
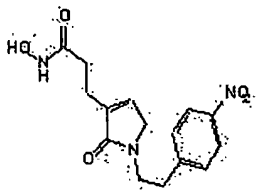
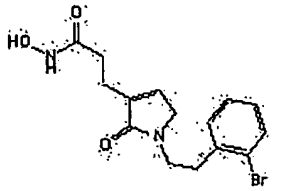
Example 38. Preparation of N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (38y)

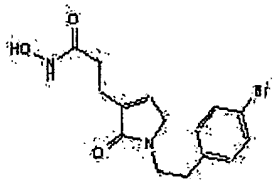
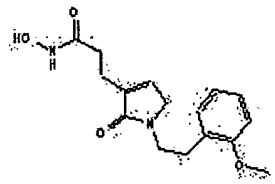
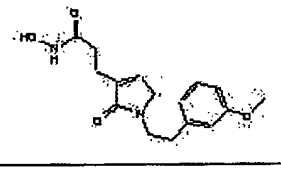
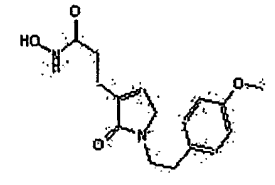
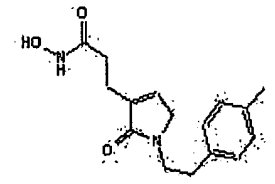
N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (38y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 39. Preparation of N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (39y)

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (39y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

[Table 6]

Example	Chemical structure	NMR spectrum data
29		7.25-7.18 (m, 1H), 6.90 (ab, J= 18.3 Hz, 4.3 Hz, 3H), 6.71 (br t, 1H), 3.65 (t, J= 6.9 Hz, 4H), 2.85 (t, J= 6.9 Hz, 2H), 2.61 (s, 2H), 2.45 (s, 2H)
30		7.11-6.94 (m, 4H), 6.70 (br t, 1H), 3.65 (s, 4H), 2.82 (s, 3H), 2.68-2.60 (m, 3H)
31		7.93 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 6.7 Hz, 1H), 7.44-7.36 (m, 2H), 6.81 (br t, 1H), 3.85 (s, 2H), 3.76 (t, J= 7.3 Hz, 2H), 3.15 (t, J= 7.1 Hz, 2H), 2.54 (t, J= 7.1 Hz, 2H), 2.30 (t, J= 7.4 Hz, 2H)
32		8.00 (d, J= 7.2 Hz, 2H), 7.49-7.38 (m, 2H), 6.70 (br t, 1H), 3.72 (s, 2H), 3.64 (t, J= 7.2 Hz, 2H), 2.93 (t, J= 7.4 Hz, 2H), 2.48 (t, J= 7.3 Hz, 2H), 2.22 (t, J= 7.7 Hz, 2H)
33		8.09 (d, J= 8.4 Hz, 2H), 7.36 (d, J= 9.6 Hz, 2H), 6.74 (br t, 1H), 3.76 (d, J= 1.2 Hz, 1H), 3.69(t, J= 7.1Hz, 1H), 3.29 (d, J= 7.8 Hz, 1H), 3.26 (dd, J= 1.8 Hz, 1.5 Hz, 1H), 2.97 (t, J= 7.3 Hz, 2H), 2.49 (t, J= 6.9 Hz, 2H), 2.25 (t, J= 7.6 Hz, 2H)
34		7.48 (d, J= 8.1 Hz, 2H), 7.21-7.13 (m, 2H), 7.07-7.02 (m, 1H), 6.71 (br t, 1H), 3.70-3.62 (m, 4H), 2.98 (t, J= 7.3 Hz, 2H), 2.52 (t, J= 7.3 Hz, 2H), 2.27 (t, J= 7.6 Hz, 2H)

Example	Chemical structure	NMR spectrum data
35		7.40 (d, J= 8.4 Hz, 2H), 7.10 (d, J= 8.1 Hz, 2H), 6.79 (br t, 1H), 3.78 (d, J= 1.2 Hz, 2H), 3.66 (t, J= 7.3 Hz, 2H), 2.85 (t, J= 7.1 Hz, 2H), 2.54 (t, J= 7.1 Hz, 2H), 2.30 (t, J= 7.4 Hz, 2H)
36		7.19-7.13 (m, 1H), 7.03-7.01 (m, 1H), 6.81(t, J= 7.4 Hz, 2H), 6.70 (br t, 1H), 3.78(s, 3H), 3.69 (s, 2H), 3.63 (t, J= 7.0 Hz, 2H), 2.85 (t, J= 7.1 Hz, 2H), 2.52 (t, J= 7.7 Hz, 2H), 2.27 (t, J= 7.6 Hz, 2H)
37		7.14(t, J= 7.6 Hz, 1H), 6.72-6.67 (m, 4H), 3.72 (s, 3H), 3.65 (s, 2H), 3.60 (br t, 2H), 2.80 (t, J= 7.1 Hz, 2H), 2.51 (t, J= 7.3 Hz, 2H), 2.25 (t, J= 7.3 Hz, 2H)
38		7.02 (d, J= 8.7 Hz, 2H), 6.76 (d, J= 8.4 Hz, 2H), 6.66 (br t, 1H), 3.72 (s, 3H), 3.62-3.56 (m, 4H), 2.76 (t, J= 7.3 Hz, 2H), 2.51 (t, J= 7.3 Hz, 2H), 2.25 (t, J= 7.6 Hz, 2H)
39		7.05 (s, 4H), 6.74 (br t, 1H), 3.72 (d, J= 1.2 Hz, 2H), 3.64 (t, J= 7.3 Hz, 2H), 3.31-3.29 (m, 2H), 2.82 (t, J= 7.3 Hz, 2H), 2.54 (t, J= 7.1 Hz, 2H), 2.31 (d, J= 7.8 Hz, 2H), 2.27 (s, 3H),

Example 40. Preparation of N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (40ah)

Step 1. Preparation of 3-*p*-tolyl-acrylic acid methyl ester (40aa)

1g of *p*-tolualdehyde (8.3mM) and 4.16g of triphenyl phosphanyliden-acetic acid methyl ester (12.45mM) were dissolved in methylene chloride, the reaction solution was stirred at 90°C for overnight. After the resluting mixture was concentrated under reduced pressure, a solvent mixture mixed with EtOAc and hexane(1:7) was added thereto with stirring for 1hr. And then white solid was removed on filter, the residue was filtered and concentrated *in vacuo* to give 1.39g of 3-*p*-tolyl-acrylic acid methyl ester (40aa) (yield : 95%).

Step 2. Preparation of 3-*p*-tolyl-propionic acid methyl ester (40ab)

1.39g of 3-*p*-tolyl-acrylic acid methyl ester (40aa) prepared by above Step 1 was dissolved in methanol solution (7.9 mM) under nitrogen atmosphere. Then Pd-C was added thereto, hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexane (1:10) as an eluant to give 1.24g of 3-*p*-tolyl-propionic acid methyl ester (40ab) (yield : 95%).

Step 3. Preparation of 3-*p*-tolyl-propane-1-ol (40ac)

1.24g of 3-*p*-tolyl-propionic acid methyl ester (40ab) prepared by above Step 2 was dissolved in 100 ml of tetrahydrofuran under Ar atmosphere. Then 27ml of lithium alluminium-hydride was added thereto with stirring for 2hrs at 0°C. After 3ml of distilled water, 3ml of NaOH (1N) and 9ml of distilled water were added to the reaction mixture sequentially, the mixture was stirred for 30min and filtered using cellite in glass filter and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:2) as an eluant to give 971mg of 3-*p*-tolyl-propane-1-ol (40ac) (yield : 93%).

Step 4. Preparation of toluene-4-sulfonate-3-*p*-tolyl-propyl ester (40ad)

2.46g of tosyl chloride (13 mM), 3.4ml of diisopropylamine (19.4 mM) and 158mg of 4-(dimethylamino)pyridine (1.29 mM) were added to reaction solution (6.46mM) dissolving 971mg of 3-*p*-tolyl-propane-1-ol (40ac) prepared by above step 3 in methylene chloride at 0°C under Ar atmosphere with stirring for 6hrs, and the reaction mixture was stirred for 12 hrs at room temperature. After the reaction mixture was neutralized with ammonium chloride, the mixture was extracted with ethyl acetate, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:7) as an eluant to give 1.3g of toluene-4-sulfonate-3-*p*-tolyl-propyl ester (40ad) (yield : 70%).

Step 5. Preparation of allyl-(3-*p*-tolyl-propyl)-amine (40ae)

1.6ml of allylamine (21.4mM) and 0.97ml of diisopropyl ethylamine (5.5mM) were added to the reaction solution (4.27 mM) containing 1.3g of allyl-(3-*p*-tolyl-propyl)-amine (40ae) prepared by above Step 4 dissolved in acetonitrile solution with stirring for 6 hrs at 100 °C. After the reaction mixture was neutralized with 10% NaOH

solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 687 mg of allyl-(3-*p*-tolyl-propyl)-amine (40ae) (yield : 85%).

Step 6. Preparation of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af)

683 mg of 2-methylene-pentane dionate-5-methyl ester (4.3 mM), 902mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (4.7 mM) and 133mg of 4-(dimethylamino)pyridine (1.09 mM) were added to reaction solution (3.62mM) dissolving 687mg allyl-(3-*p*-tolyl-propyl)-amine (40ae) prepared by above step 5 in 0.5M of methylene chloride solution under Ar atmosphere and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with saturated 10ml of $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 797 mg of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af) (yield : 73%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ7.05(s, 4H), 5.70(s, 1H), 5.16-5.07(m, 4H), 3.94(s, 2H), 3.64(t, J=3.3Hz, 3H), 3.36(s, 2H), 2.67-2.51(m, 6H), 2.28(s, 3H), 1.83(t, J=7.7Hz, 2H)

Step 7. Preparation of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag)

797mg of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af) (2.6mM) prepared by the above Step 6 was added to the catalyst solution containing 180mg of ruthenium catalyst (0.1mM) dissolved in 200ml of CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 391 mg of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 4H), 6.56 (s, 1H), 3.67 (s, 2H), 3.55 (s, 3H), 3.37 (t, J= 7.2 Hz, 2H), 2.48 (t, J= 8.2 Hz, 6H), 2.19 (s, 3H), 1.76 (t, J= 7.6 Hz, 2H)

Step 8. Preparation of N-hydroxy-3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (40ah)

100mg of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag) prepared by the above Step 7 was dissolved in methanol solution (0.33 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.82 ml, 5.0 mM) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 50 mg of N-hydroxy-3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (40ah) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 4H), 6.95 (s, 1H), 3.96 (s, 2H), 3.60 (s, 2H), 2.72 (s, 5H), 2.45 (s, 3H), 1.99 (s, 2H)

Example 41. Preparation of N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (41ah)

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (41ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 42. Preparation of N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (42ah)

N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (42ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 43. Preparation of N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (43ah)

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (43ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 44. Preparation of 3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (44ah)

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (44ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 45. Preparation of 3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (45ah)

3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (45ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 46. Preparation of N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (46ah)

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (46ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

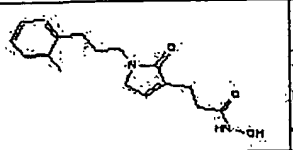
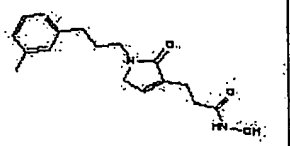
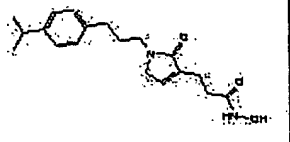
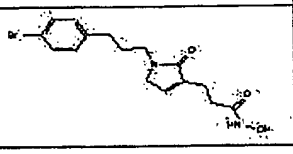
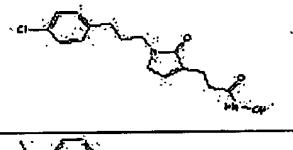
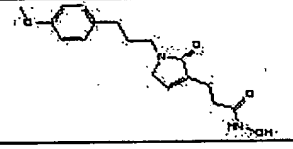
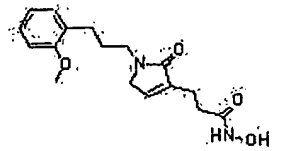
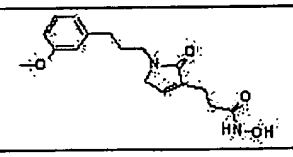
Example 47. Preparation of N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (47ah)

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (47ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 48. Preparation of N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (48ah)

N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (48ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

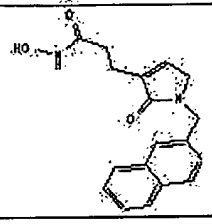
[Table 7]

Example	Chemical structure	NMR spectrum data
41		7.08 (d, J= 4.2 Hz, 4H), 6.69 (s, 1H), 3.80 (s, 2H), 3.48 (d, J= 6.6 Hz, 2H), 2.57 (d, J= 9.0 Hz, 6H), 2.25 (d, J= 6.3 Hz, 4H), 1.79 (s, 2H)
42		7.02-6.97 (m, 1H), 6.81 (d, J= 8.4 Hz, 3H), 6.64 (s, 1H), 4.07 (s, 2H), 3.71 (s, 2H), 3.32 (t, J= 7.4 Hz, 2H), 2.43 (t, J= 7.7Hz, 5H), 2.17 (t, J= 6.5 Hz, 4H), 1.78-1.68 (m, 2H)
43		10.23 (s, 1H), 7.09 (dd, J= 6.0 Hz, 4H), 6.73 (s, 1H), 3.79 (s, 2H), 3.45 (t, J= 5.1 Hz, 2H), 2.87-2.80 (m, 1H), 2.61 (s, 1H), 2.56 (t, J= 5.9 Hz, 2H), 2.46 (s, 2H), 1.88-1.81 (m, 2H), 1.26-1.19 (m, 6H)
44		7.23 (t, J= 5.5 Hz, 1H), 7.14 (t, J= 5.5 Hz, 3H), 6.73 (s, 1H), 3.77 (s, 2H), 3.43 (t, J= 5.0 Hz, 2H), 2.58 (t, J= 5.7 Hz, 4H), 2.45 (s, 2H), 1.88-1.81 (m, 2H)
45		7.23-7.04 (m, 4H), 6.73 (s, 1H), 3.77 (s, 2H), 3.43 (t, J= 5.7 Hz, 2H), 2.56 (t, J= 12.9 Hz, 3H), 2.42 (s, 2H), 1.83 (t, J= 6.7 Hz, 2H)
46		7.03 (d, J= 8.7 Hz, 2H), 6.79-6.75 (m, 2H), 6.72 (s, 1H), 3.72 (d, J= 9.9 Hz, 5H), 3.40 (t, J= 7.3 Hz, 2H), 2.58-2.42 (m, 6H), 1.78 (t, J= 7.4 Hz, 2H)
47		7.16-7.06 (m, 2H), 6.84-6.67 (m, 3H), 3.79 (t, J= 5.5 Hz, 2H), 3.75 (t, J= 3.4Hz, 3H), 3.50-3.41 (m, 2H), 2.55 (t, J= 7.7Hz, 3H), 2.43 (s, 1H), 1.87 (s, 2H), 1.84-1.77 (m, 2H)
48		7.19-7.10 (m, 1H), 6.71 (d, J= 10.8Hz, 4H), 3.75 (s, 5H), 3.49-3.40 (m, 2H), 2.55 (t, J= 7.7Hz, 4H), 2.43 (s, 2H), 1.88-1.84(m, 2H)

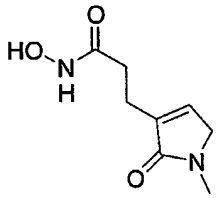
Example 49. Preparation of N-hydroxy-3-(1-naphthalene-2-ylmethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (1e')

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (1e') was prepared by the similar procedure described in above Example 1 (*See* Table 8).

[Table 8]

Example	Chemical structure	NMR spectrum or LC-MS data
49		RT : 3.93-5.93 (Mass : 311.2)

Example 50. Preparation of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h')



Step 1. Preparation of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2f)

0.1ml of triethylsilane (0.63mM) was added to the reaction solution containing 200mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.63 mM) dissolved in 0.7ml of trifluoroacetic acid solution at 0°C. After the reaction mixture was heated for 1hr, the mixture was filtered and concentrated *in vacuo* to remove solvent. Then the resulting mixture was dissolved in 20ml of chloroform solution to separate into an organic layer and water layer. The organic layer was washed with 5ml of saturated $NaHCO_3$ solution and 5ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (19:1) as an eluant to give 50 mg of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2f) (yield : 47%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.76 (br t, 1H), 3.89 (d, J= 1.3 Hz, 2H), 3.63 (t, J= 1.9 Hz, 3H), 2.58 (s, 4H)

Step 2. Preparation of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g)

0.33ml of NaHMDS solution (1.0 M in THF, 0.33mM) was added to 0.6ml of THF solution containing 50mg of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid

methyl ester (2f) (0.295mM) prepared by the Step 1 in a dropwise manner at -79°C and stirred for 30 mins. After 0.3ml of dimethyl sulfate 0.359mM) was added thereto, the reaction mixture was stirred for 4hrs at 0°C. Then the resulting mixture was dissolved in 2ml of saturated NH_4Cl solution and extracted with 7ml of ethyl acetate to separate into an organic layer and water layer. The organic layer was washed with 2ml of saturated $NaHCO_3$ solution and 2ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with EtOAc as an eluant to give 18 mg of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g) (yield : 33%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.65 (br t, 1H), 3.81 (s, 1H), 3.64 (s, 3H), 3.01 (s, 3H), 2.60 (t, 4H).

Step 3. Preparation of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h)

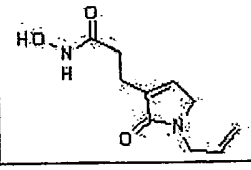
18mg of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g) prepared by the above Step 2 was dissolved in methanol solution (0.1 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.09 ml, 0.15 mM) was added thereto at 0°C and the resulting mixture was stirred for 1 hr at room temperature. The resulting mixture was neutralized with 0.03 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and methanol (5:2) as an eluant to give 11 mg of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h) (yield : 59%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.76 (br t, 1H), 3.84 (s, 2H), 3.00 (s, 3H), 2.59 (t, J= 7.2 Hz, 2H), 2.42 (t, J= 7.2 Hz, 2H)

Example 51. Preparation of 3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (3h')

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (3h') was prepared by the similar procedure described in above Example 50 (*See* Table 9).

[Table 9]

Example	Chemical structure	NMR spectrum data
51		6.89 (br t, 1H), 5.98-5.67 (m, 2H), 5.10-5.08 (m, 1H), 3.36 (t, J= 1.8Hz, 2H), 2.61 (s, 2H), 2.06 (s, 2H), 1.87 (s, 2H)

Example 52. Preparation of N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4n')

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

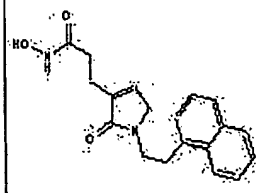
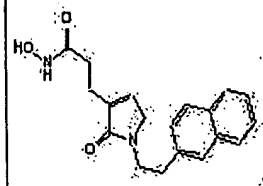
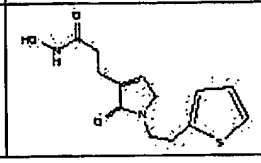
Example 53. Preparation of N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5n')

N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

Example 54. Preparation of N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6n')

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

[Table 10]

Example	Chemical structure	NMR spectrum data
52		8.01(d, J= 8.1 Hz, 1H), 7.77(d, J= 8.7 Hz, 1H), 7.66 (d, J= 8.1 Hz, 1H), 7.48-7.20 (m, 4H), 6.62 (br t, 1H), 3.56 (s, 2H), 3.30-3.25(m, 2H), 2.51 (t, J= 7.3 Hz, 2H), 2.25 (t, J= 7.3 Hz, 2H)
53		7.73-7.66 (m, 3H), 7.53 (s, 1H), 7.40-7.32 (m, 2H), 7.22 (s, 1H), 6.61 (br t, 1H), 3.69 (t, J= 7.3 Hz, 2H), 3.60 (s, 2H), 2.97 (t, J= 7.0 Hz, 2H), 2.49 (t, J= 7.2 Hz, 2H), 2.24 (t, J= 7.3 Hz, 2H)
54		7.08 (br t, 1H), 6.85 (t, J= 4.0 Hz, 1H), 6.74 (s, 1H), 6.68 (br t, 1H), 3.65 (s, 4H), 3.37-3.29 (m, 1H), 3.05 (t, J= 6.1 Hz, 2H), 2.51 (d, J= 4.8 Hz, 2H), 2.28 (s, 1H)

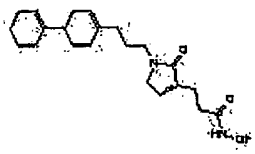
Example 55. Preparation of 3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (7w')

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (7w') was prepared by the similar procedure described in above Example 40 (*See* Table 11).

Example 56. Preparation of N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8w')

N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8w') was prepared by the similar procedure described in above Example 40 (*See* Table 11).

[Table 11]

Example	Chemical structure	NMR spectrum data
55		7.51 (dd, J= 8.0 Hz, 4H), 7.37 (t, J= 7.4 Hz, 2H), 7.26 (q, J= 7.2 Hz, 3H), 6.81 (s, 1H), 4.79 (s, 2H), 3.89 (s, 2H), 3.48 (t, J= 7.1 Hz, 2H), 2.64 (t, J= 7.7 Hz, 2H), 2.56 (t, J= 5.1 Hz, 2H), 2.32 (t, J= 6.9 Hz, 1H)
56		10.54 (s, 1H), 7.71 (dd, J= 7.9 Hz, 3H), 7.54 (s, 1H), 7.41-7.33 (m, 2H), 7.24(d, J= 7.8 Hz, 1H), 6.64 (s, 1H), 3.67 (s, 2H), 3.40 (s, 2H), 2.69 (t, J= 6.7 Hz, 2H), 2.57 (s, 2H), 2.41 (s, 2H), 1.86 (s, 2H)

Example 57. Preparation of 3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydropyridin-3-yl]N-hydroxypropionamide(e1)

Step 1. Preparation of But-3-enyl-(2,4-dimethoxybenzyl)amine (b)

0.5ml of 1-Bromo-3-butene (4.926mM) and 0.94 ml of diisopropyl ethylamine (5.396 mM) were added to the reaction solution containing 0.74ml of 2, 4-dimethoxybenzylamine(a) (4.926 mM) dissolved in methylene chloride with stirring and the solution was left alone at room temperature for overnight. The reaction mixture was washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with EtOAc solvent as an eluant to give 436mg of the pure title compound (b) (yield: 40%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.10(d, J=8.1 Hz, 1H), 6.41(m, 2H), 5.75(m, 1H), 5.01(m, 2H), 3.78(s, 3H), 3.77(s, 3H), 3.70(s, 2H), 2.63(t, J=7.5 Hz, 2H), 2.24(m, 2H)

Step 2. Preparation of 4-[But-3-enyl-(2,4-dimethoxybenzyl)-carbamoyl]-pent-4-enoic acid methyl ester (c)

714 mg of 2-methylene-pentane dionate-5-methyl ester (4.519 mM), 953mg of EDC (4.971 mM) and 110mg of DMAP (0.9 mM) were added to 0.5 M of reaction solution dissolving the compound (b) prepared by above step 1 in methylene chloride and the mixture was stirred for 5 hrs at room temperature. The resulting mixture was diluted with ethyl acetate and washed with 5% HCl solution (10 ml) and 10ml of sat. $NaHCO_3$ solution to separate into an organic layer and water layer. The organic layer

was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 1.39 g of 4-[but-3-enyl-(2,4-dimethoxybenzyl)-carbamoyl]-pent-4-enoic acid methyl ester (c) (yield : 40%).

Step 3. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d)

130mg of the compound (c) (0.360 mM) prepared by the above Step 2 was added to the catalyst solution containing 20mg of ruthenium (0.024 mM) dissolved in CH_2Cl_2. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with methanol/chloroform (1:10) solvent mixture as an eluant to give 108 mg of the title compound (d) (yield : 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17(d, J=8.9Hz, 1H), 6.41(m, 2H), 6.26(t, J=4.3 Hz, 1H), 4.53(s, 2H), 3.77(s, 3H), 3.76(s, 3H), 3.62(s, 3H), 3.28(t, J=7.1 Hz, 2H), 2.61-2.47(m, 4H), 2.22(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.6, 164.8, 160.2, 158.5, 134.2, 133.9, 130.4, 118.0, 104.1, 98.3, 55.2, 51.3, 45.0, 44.3, 33.3, 26.6, 23.9

Step 4. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-propionamide (e1)

46mg of compound (d) prepared by the above Step 3 was dissolved in methanol solution (0.138 mM) and then 1,7 M methanolic suspension solution containing NH_2OK (0.122 ml, 0.207 mM) was added thereto at 0°C and the resulting mixture was stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate solution, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:10) solvent mixture as an eluant to give 32 mg of the title compound (e1) (yield: 73%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.122(d, J=9.0 Hz, 1H), 6.415-6.331 (m, 3H), 4.505 (s, 2H), 3.750 (s, 3H), 3.744 (s, 3H), 3.271 (t, J=6.9 Hz, 2H), 2.552 (m, 2H), 2.381 (m, 2H), 2.220 (m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1, 165.4, 160.2, 158.5, 135.8, 133.5, 130.4, 117.5, 104.2, 98.3, 55.3, 44.9, 44.6, 32.8, 27.1, 23.8

Example 58. Preparation of N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (e2)

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (e2) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

Example 59. Preparation of N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e3)

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e3) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

Example 60. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide (e4)

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide (e4) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

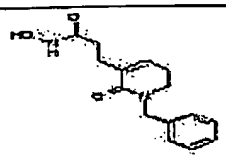
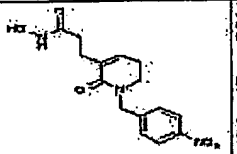
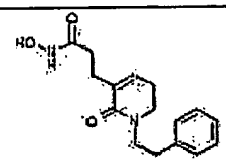
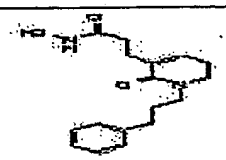
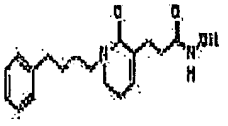
Example 61. Preparation of N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (e5)

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (e5) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

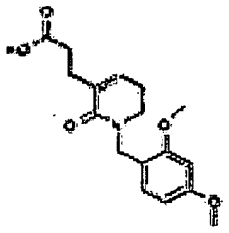
Example 62. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e6)

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e6) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

[Table 12]

Example	Chemical structure	NMR spectrum data
58		7.28(m, 5H), 6.44(t, J=4.3 Hz, 1H), 4.61(s, 2H), 3.33(m, 2H), 2.57(t, J=7.5 Hz, 2H), 2.28(m, 4H)
59		8.14(d J=8.4Hz 2H), 7.40(t J=7.2Hz 2H), 6.42(br t 1H), 4.67(s 2H), 3.32(t J=6.3Hz 2H), 2.67-2.32(m 6H)
60		7.29-7.18(m 5H) 6.40(br t 1H), 3.62(t J=7.2Hz 2H), 3.19(t J=7.1Hz 2H), 2.85(t J=7.1Hz 2H), 2.54-2.44(m 2H), 2.18-2.15(m 4H)
61		7.24-7.11(m, 5H), 6.31(br t, 1H), 3.35(br t, 2H), 3.23(br t, 2H), 2.55(d, J=6.6Hz, 4H), 2.33(s, 2H), 2.18(s, 2H), 1.80(br t, 2H)
62		7.28-7.13(m, 5H), 6.36(t, J=3.9, 1H), 3.39(t, J=6.75, 2H), 3.29(t, J=7.05, 2H), 2.62(t, J=7.05, 2H), 2.54(t, J=6.75, 2H) 2.40(t, J=6.75, 2H), 2.27(ab, J=6.0, 5.4, 2H), 1.58(t, J=2.7, 4H)

Example 63. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f1)



11mg of $LiOH \cdot H_2O$ solution (0.262 mM) was added to 0.75ml of THF solution containing 58mg of 3-[1-(2,4-dimethoxy benzyl)-2-oxo-1,2,5,6-tetrahydro pyridine-3-yl]-propionic acid methyl ester (d) (0.174 mM) in a dropwise manner at 0°C. After the reaction mixture was stirred for 2hrs at 0°C and for 1hr at room temperature, 5% HCl was added to the mixture to pH 2. Then the mixture was extracted three times with

10ml of ethyl acetate, the organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with methanol/chloroform (1:10) solvent mixture as an eluant to give 44 mg of the title compound (f1) (yield : 80%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16(d, J=8.9 Hz, 1H), 6.42(m, 2H), 6.29(t, J=4.3 Hz, 1H), 4.54(s, 2H), 3.76(s, 3H), 3.76(s, 3H), 3.29(t, J=7.2 Hz, 2H), 2.56(m, 4H), 2.22(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.7, 165.1, 160.1, 158.5, 134.6, 133.9, 130.5, 117.7, 104.1, 98.3, 55.2, 44.9, 44.5, 33.5, 26.3, 23.8

Example 64. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f2)

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f2) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

Example 65. Preparation of 3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f3)

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f3) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

Example 66. Preparation of 3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f4)

3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f4) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

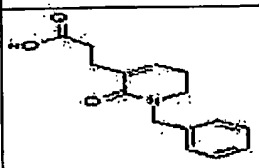
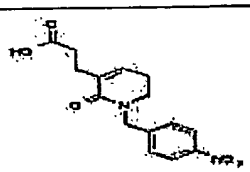
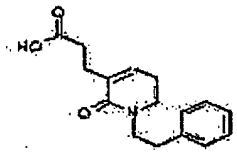
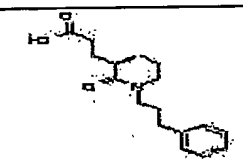
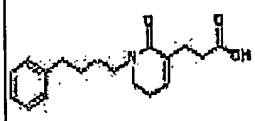
Example 67. Preparation of 3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f5)

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f5) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

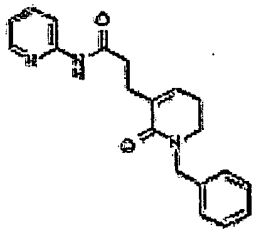
Example 68. Preparation of 3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f6)

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f6) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

[Table 13]

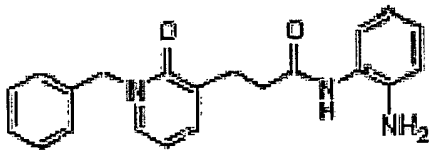
Example	Chemical structure	NMR spectrum data
64		7.25(m, 5H), 6.34(t, J=4.2Hz, 1H), 4.60(s, 2H), 3.26(t, J=7.1 Hz, 2H), 2.59(m, 4H), 2.25(m, 2H)
65		8.16(d J=8.7Hz 2H), 7.42(d, J=8.6Hz, 2H), 6.39(t J=4.3Hz, 1H) 4.69(s, 2H) 3.32(t, J=7.2Hz, 2H) 2.64-2.53(m, 4H), 2.33(dd J=6.9Hz, 5.7Hz, 2H)
66		9.92(br s 1H), 7.28-7.15(m, 5H), 6.28(t, J=4.4, 1H), 3.60(t J=7.4, 2H) 3.16(t, J=7.2, 2H) , 2.84(t, J=7.4, 2H) 2.58-2.48 (m, 4H) 2.15(AB, J=11.4, 6.8, 2H)
67		7.28-7.10(m,5H), 6.28(br, t, 1H), 5.75-5.60(m, 1H), 5.01(d, J=16.5Hz, 2H), 3.41-3.26(m, 3H) 2.63-2.26(m, 7H) 1.84(t, J=6.8Hz, 2H)
68		7.256-7.138(m, 5H), 6.33(br, t, 1H), 3.42(t, J=6.9, 2H), 3.32(t, J=7.35, 2H), 2.63(t, J=7.05, 2H), 2.547(d, J=2.4, 4H), 2.30(d, J=4.5, 2H), 1.61(q, J=1.5, 4H)

Example 69. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide (g1)



Pyridyl amine was added to organic solvent dissolving 30mg of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (0.12mM) in EDC. The resulting compound was purified by Silica gel column chromatography with methanol/chloroform (1:20) solvent mixture as an eluant to give 16 mg of the title compound (g1) (yield : 39%).

Example 70. Preparation of N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g2)



40mg of 1,2-phenylenediamine (0.37 M), 77mg of EDC (0.4 M) and 1mg of DMAP (3 M%) were added to reaction solution dissolving 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid prepared by above Example 8 in 1ml of methylene chloride under Argon atmosphere. After the mixture was stirred for 13 hrs at room temperature, the resulting mixture was diluted with ethyl acetate and washed with 10% NaOH solution (10 ml). Then the residue was extracted with 50ml of chloroform, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:20) as an eluant to give 96 mg of N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g2) (yield : 91%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ8.29 (s, 1H), 7.29-7.19 (m, 5H), 7.13 (d, 1H, *J*=7.8Hz), 6.99-6.94 (m, 1H), 6.68 (t, 2H, *J*=7.9Hz), 6.37 (t, 1H, *J*=8.4Hz), 4.57 (t, 2H, *J*=7.4Hz), 3.88 (s, 2H), 3.29-3.21 (m, 2H), 2.68 (t, 2H, *J*=6.5Hz), 2.59 (t, 2H, 6.5Hz), 2.26-2.217 (m, 2H)

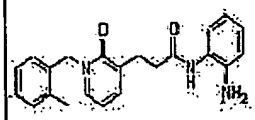
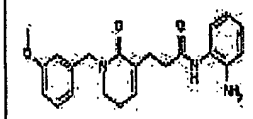
Example 71. Preparation of N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g3)

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g3) was prepared by the similar procedure described in above Example 69 and 70 (*See* Table 14).

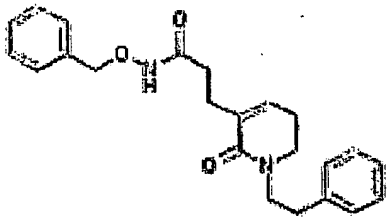
Example 72. Preparation of N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g4)

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g4) was prepared by the similar procedure described in above Example 69 and 70 (*See* Table 14).

[Table 14]

Example	Chemical structure	NMR spectrum data
71		8.23(s,1H), 7.12(dd,5H,*J*=6.6Hz), 6.979(t,1H,*J*=7.5Hz), 6.697(t,2H,*J*=8.9Hz), 6.408(t,1H,*J*=7.4Hz), 4.602(s,2H), 3.874(s,2H), 3.239(t,2H,*J*=7.1Hz), 2.702(t,2H,*J*=6.8Hz), 2.604(t,2H,*J*=6.3Hz), 2.260(t,5H,*J*=6.3Hz)
72		8.305(s,1H), 7.189-7.091(m,2H), 6.969-6.914(m,2H), 6.794-6.741(m,3H), 6.691-6.631(m,2H), 6.355(t,1H,*J*=4.1Hz), 4.539(s,2H) 3.965(s,2H), 3.707(s,3H), 3.253(t,2H,*J*=7.0Hz), 2.661-2.539(m,4H), 2.22(dd,2H,*J*=7.1Hz)

Example 73. Preparation of N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g5)



Benzyloxyamine was added to organic solvent dissolving 30mg of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (0.15mM) prepared by above Example 12 in EDC. The resulting compound was purified by Silica gel column chromatography with ethylacetate/chloroform (1:1) solvent mixture as an eluant to give 41 mg of N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g5) (yield : 75%).

^{1}H-NMR (300 MHz, CDCl3) δ7.41-7.15 (m, 1H), 6.34 (br t, 1H), 4.88 (s, 2H), 3.58 (t, *J*=7.4Hz, 2H), 3.16 (t, *J*=7.2Hz, 2H), 2.82 (t, *J*=7.2Hz, 2H), 2.53 (t, *J*=6.8 Hz, 2H), 2.26 (br s, 1H), 2.19 (dd, *J*=11.4, 7.1Hz, 2H)

Example 18. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)

Step 1. Preparation of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (h)

50mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d) (0.16 mM) prepared by the Step 3 of above Example 1 was dissolved in methanol solution at room temperature. Then 154mg of Zn (2.36mM) and 0.01ml of acetic acid (0.16 mM) were added thereto and the mixture was stirred for 20 hrs at 80°C. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with ethylacetate and hexane (1:1) as an eluant to give 43 mg of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (h) (yield : 92%).

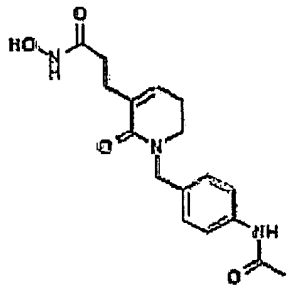
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (d, 1H, J=8.5Hz), 8.11 (d, 1H, J=8.4Hz), 7.37 (t, 2H, J=8.3Hz), 6.33 (t, 1H, J=4.3Hz), 4.66 (d, 2H, J=7.5Hz), 3.63 (s, 3H), 3.29 (t, 2H, J=6.6Hz), 2.63 (t, 2H, J=6.9Hz), 2.54 (t, 2H, J=6.6Hz), 2.28 (t, 2H, J=4.2Hz)

Step 2. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i)

17.5mg of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (h) prepared by above Step 1 was dissolved in methylene chloride solution (0.06mM). And then 6 μl of $(AcO)_2O$(0.07 mM), 0.01ml of triethylamine (0.08mM) and 1.0mg of DMAP (0.008mM) were added thereto and the mixture was stirred for 3 hrs at 0°C. The reaction was stopped by adding methanol and the mixture was extracted three times with 10ml of ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with ethylacetate as an eluant to give 46 mg of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i) (yield : 44%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ8.34 (s, 1H), 7.40 (d, 2H, J=8.4Hz), 7.10 (d, 2H, J=8.4Hz), 6.29 (t, 1H, J=4.2Hz), 4.50 (s, 2H), 3.61 (s, 3H), 3.22 (t, 2H, J=7.1Hz), 2.59 (t, 2H, J=7.1Hz), 2.51 (d, 2H, J=6.6Hz), 2.22 (dd, 2H, J=6.9Hz), 2.09 (s, 3H)

Step 3. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)



3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i) prepared by above Step 2 dissolved in organic solvent such as methanol was reacted with amine salt to give 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (d J=8.0Hz 2H), 7.23 (d J=8.0Hz 2H), 6.44 (br t 1H), 4.57 (S 2H), 3.33 (t, J=6.5Hz, 6H) 2.57 (br t, 2H) 2.30-2.26 (m, 4H) 2.10 (s, 2H)

Example 75. Preparation of N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide (j2)

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide (j2) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

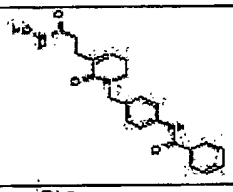
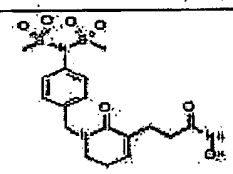
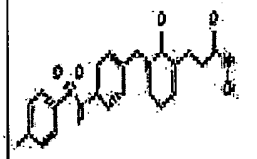
Example 76. Preparation of N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j3)

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j3) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

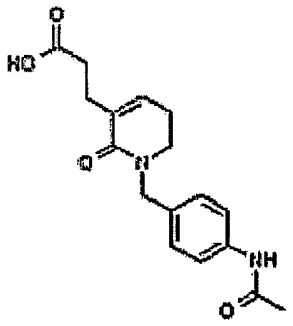
Example 77. Preparation of N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j4)

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j4) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

[Table 15]

Example	Chemical structure	NMR spectrum data
75		7.90 (t, J=7.05Hz, 2H), 7.67 (d, J=8.10Hz, 2H) 7.59-7.47(m, 3H) 7.30 (d J=8.10Hz 2H), 6.45 (br t, 1H) 4.61 (s,2H) 3.36 (t, J=7.2, 2H) 3.30 (q, J=1.5Hz, 4H) 2.58 (br t,2H)
76		7.24 (q, J=8.6Hz, 4H) 6.45 (br t, 1H) 4.58 (s,2 H) 3.38-3.29 (m,7H) 2.93 (s, 3H) 2.57 (t, 2H, J=7.1) 2.34-2.24(m, 4H)
77		7.78 (d, J=8.0Hz, 2H), 7.31 (d, J=7.5Hz,2H) 7.27-7.21 (m, 4H) 6.97 (t,J=7.2Hz,1H) 4.61(d, J=3.5Hz, 1H) 3.47(s, 4H) 3.3 6-3.30 (m,1H) 2.71-2.64(m, 1H) 2.51-2.44 (m,3H), 2.32 (d, J=4.5Hz, 1H)

Example 78. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k)



3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (i) prepared by above Step 2 of Example 18 dissolved in organic solvent such as tetrahydrofurane was reacted with LiOH to give 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (d J=8.0Hz 2H), 7.23 (d J=8.6Hz 2H), 6.45 (t J=4.5Hz 1H), 4.58 (S 2H), 3.32 (t, J=7.5Hz,3H) 2.57 (t, J=7.5Hz, 2H) 2.46 (t, J=7.5Hz, 2H)

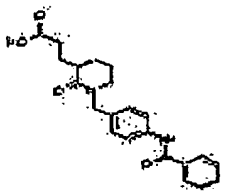
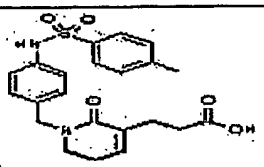
Example 79. Preparation of 3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k2)

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k2) was prepared by the similar procedure described in above Example 78 (*See* Table 16).

Example 80. Preparation of 3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k3)

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k3)was prepared by the similar procedure described in above Example 78 (*See* Table 16).

[Table 16]

Example	Chemical structure	NMR spectrum data
79		7.83 (d, J=6.9Hz, 2H), 7.59(d, J=8.4Hz, 2H), 7.49-7.37 (m, 4H), 7.19 (d, J=8.4Hz, 2H), 6.33 (d, J=4.5Hz, 1H) 3.26 (t, J=7.2Hz, 3H) 2.54-2.40 (m, 4H) 2.24 (ab, J=11.6Hz, 3.5Hz, 2H)
80		7.74(d, J=8.1Hz, 4H), 7.18 (d, J=7.8Hz,2H), 6.93 (d, J=8.1, 2H), 4.53(s, 2H), 3.20(br t,2H), 2.40 (s, 9H)

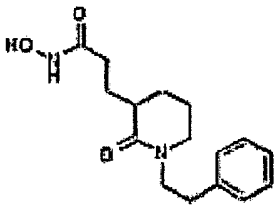
Example 81. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m)

Step 1. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l)

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in alcohol solvent under nitrogen atmosphere. Then Pd-C was added thereto, and the mixture was hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with EtOAc/hexane (1:1) as an eluant to give [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l) (yield : 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 1H, *J*=8.4Hz), 6.42 (d, 2H, *J*=7.2Hz), 4.51(ab, 2H, *J*=32.9, 7.4Hz), 3.76 (s, 6H), 3.66(s, 3H), 3.24-3.18(m, 2H), 2.93-2.72(m, 2H), 2.56-2.43(m, 1H), 1.98-1.55(m, 4H)

Step 2. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m)



[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l) prepared by above Step 1 was reacted with amine salt to give N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26-7.17 (m 5H), 3.61-3.44 (m 2H) 3.08-2.83 (m 4H), 2.56-2.16 (m 4H)

Example 82. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1)

Step 1. Preparation of 3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n)

2-Methylene-pentane dionate-5-methyl ester, EDC and DMAP were added to reaction solution dissolving the but-3-enyl-(2,4-dimethoxybenzyl)amine (b) prepared by above Step 1 of Example 1 in methylene chloride and the mixture was stirred for 5 hrs at room temperature to give 3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n).

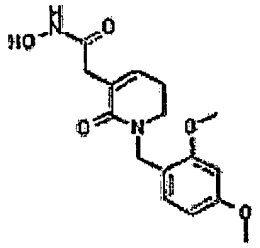
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H), 5.69(br t, 1H), 5.23(s, 2H), 5.00(t, 2H, *J*=12.6Hz), 4.74(s, 2H), 3.61(s, 3H), 3.42(s, 4H), 2.30(q, 2H, *J*=7.2Hz)

Step 2. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o)

3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n) prepared by above Step 1 was added to the catalyst solution containing Grubb's (I) catalysis such as ruthenium dissolved in organic solvent such as CH_2Cl_2 to give [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17 (d, 1H, J=6.2Hz), 6.42-6.36 (m, 3H), 4.54 (s, 2H), 3.76 (d, 6H, J=3.0Hz), 3.66 (s, 3H), 3.35(t, 2H, J=6.9), 3.28(s, 2H), 2.29(ab, 2H, J=11.3, 3.4Hz)

Step 3. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1)



[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o) prepared by above Step 2 dissolved in alcohol solvent was reacted with amine salt to give 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J=8.7Hz, 1H), 6.54(br t, 1H) 6.44 (d, J=6.0Hz, 2H), 4.55 (s, 2H), 3.78(s,6H), 3.41-3.32(m,2H), 3.20(s, 2H), 2.0 (d, J=4.5Hz, 2H)

Example 83. Preparation of 2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p2)

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p2) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

Example 84. Preparation of N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p3)

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p3) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

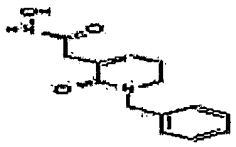
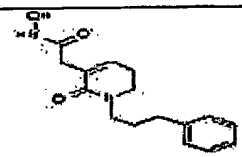
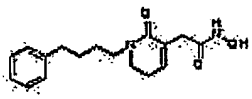
Example 85. Preparation of N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p4)

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p4) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

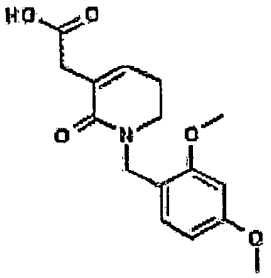
Example 86. Preparation of N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p5)

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p5) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

[Table 17]

Example	Chemical structure	NMR spectrum data
83		7.34-7.22 (m, 5H), 6.58 (t,J=4.5Hz,1H) 4.60 (s, 2H) 3.39-3.30(m,3H) 3.20 (s,2H) 2.39-2.30 (m,2H)
84		8.21 (d, J=8.7Hz, 1H), 7.44 (d, J=8.7Hz, 2H) 6.63 (t, J=4.3Hz, 1H), 4.75 (s, 2H), 3.41(ab, J=6.5Hz, 4H), 2.43(ab, J=6.2Hz, 2H)
85		7.22 (d, J=6.5Hz, 2H) 7.14(s, 3H) 6.51(br t, 1H) 3.43-3.32 (m,5H) 3.11(s, 1H) 2.59(s,2H) 2.29(s,2H) 1.84(s,2H)
86		7.28-7.13 (m,5H), 6.54(br t, 1H), 3.44-3.31 (m,5H), 3.14(s,1H) 2.62(t,J=7.1Hz,2H), 2.34(s,2H), 1.58(t, J=3.4Hz, 4H)

Example 87. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid (q1)



[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o) prepared by the Step 2 of Example 26 dissolved in TFA was reacted with LiOH to give [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid (q1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ7.18 (d, *J*=8.7Hz, 1H), 6.54 (t, *J*=4.3Hz, 1H), 6.45 (d, *J*=6.6Hz, 2H), 4.60 (s,2H), 3.79(s, 6H) 3.39(t, *J*=7.3Hz, 2H), 3.34(s, 2H), 2.32(ab, *J*=11.7Hz, 3.6Hz, 2H)

Example 88. Preparation of (1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q2)

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q2) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

Example 89. Preparation of (2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q3)

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q3) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

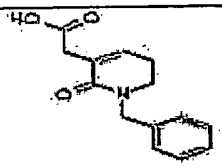
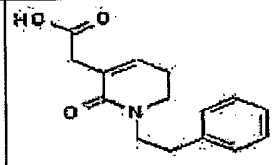
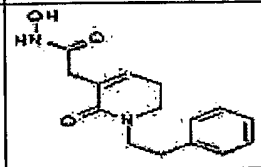
Example 90. Preparation of [2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q4)

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q4) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

Example 91. Preparation of [2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q5)

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q5) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

[Table 18]

Example	Chemical structure	NMR spectrum data
88		7.29-7.18 (m 5H) 6.50 (t, J=4.5Hz, 1H), 4.58 (s, 2H), 3.31 (d J=7.2Hz 4H), 2.29 (ab, J=11.0Hz, 3.5Hz, 2H)
89		7.31-7.18 (m,5H), 6.53 (t, J=4.5Hz, 1H), 3.67 (t, J=7.2Hz, 2H), 3.30 (s, 2H), 3.23(t,J=7.2Hz, 2H) 2.90 (t, J=7.2Hz) 2.23 (ab, J=11.7Hz,3.6Hz, 2H)
90		7.32-7.12 (m,5H) 6.47(br t, 1H) 3.56(t, J=10.8Hz, 2H), 3.11 (s,4H) 2.78(d, J=6.0Hz, 2H) 2.14(d, J=10.8Hz, 2H)
91		7.29-7.14 (m,5H), 6.55(t, J=4.2Hz, 1H), 3.46(t, J=6.7Hz, 2H), 3.38(t, J=7.3Hz, 2H), 3.31 (s, 2H) 2.64(t, J=7.1Hz, 2H) 2.37(ab, J=6.3Hz, 2H) 1.67-1.58(m,4H)

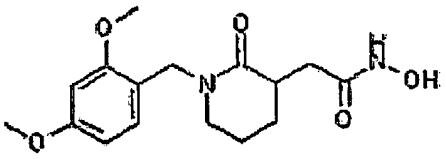
Example 92. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1)

Step 1. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r)

26mg of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester(o) (0.08mM) was dissolved in methanol solution under Ar atmosphere. 1.7mg of 10% Pd-C was added thereto and the mixture was hydrogenated under a hydrogen balloon. The reaction mixture was stirred for 5 hrs at room temperature, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography to give 25mg of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r) (yield : 99%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J= 8.4 Hz, 2H), 6.41 (dd, J= 8.4 Hz, 2H), 6.41 (s, 1H), 4.51 (dd, J=32.7, 14.9 Hz, 2H), 3.76 (s, 6H), 3.66 (s, 3H), 3.22 (dd, J= 7.5, 4.6Hz, 2H), 2.90 (dd, J=15.9, 5.1 Hz, 1H), 2.76 (m, 1H), 2.52 (dd, J=16.2, 7.5Hz, 2H), 1.98-1.55 (m, 4H)

Step 2. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1)



2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r) prepared by the Step 1 was reacted with amine salt to give [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15(d, J=9.0Hz,1H), 6.46(t, J=4.65,2H), 4.56 (q, J=7.2Hz, 23.7Hz, 2H), 3.79(s, 6H), 3.31-3.19(m, 2H), 2.86-2.69(m, 2H), 2.41(d, J=14.1Hz, 1H), 1.89-1.79 (m, 2H)

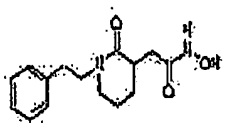
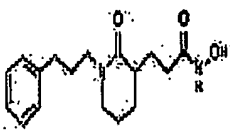
Example 93. Preparation of (2-oxo-1-phenethyl-piperidine-3-yl)-N-hydroxy-acetamide (s2)

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid (s2) was prepared by the similar procedure described in above Example 92 (*See* Table 19).

Example 94. Preparation of [2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-N-hydroxy-acetamide (s3)

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid (s3) was prepared by the similar procedure described in above Example 92 (*See* Table 19).

[Table 19]

Example	Chemical structure	NMR spectrum data
93		7.315-7.169(m,5H), 3.60(t,J=7.35,1H), 3.15(dd,J=4.8,11.1,1H), 2.917-2.856(m,1H), 2.728-2.659(m,1H), 1.698-1.426(m,4H), 1.23(d,J=7.05,5H)
94		7.29-7.12(m,5H) 3.47-3.35(m,2H) 3.29-3.23(m,2H)2.63-2.45(m,4H) 2.03-1.80(m,4H) 1.59-1.47(m,2H), 1.33-1.19(m,3H)

Example 95. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1)

Step 1. Preparation of 5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t)

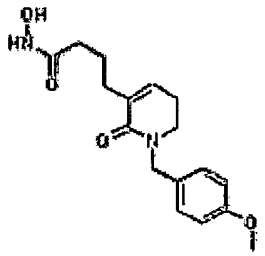
2-Methylene-pentane dionate-5-methyl ester, EDC and DMAP were added to reaction solution dissolving the but-3-enyl-(2,4-dimethoxybenzyl)amine (b) prepared by above Step 1 of Example 1 in methylene chloride solution and the mixture was stirred for 5 hrs at room temperature to give 5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t).

Step 2. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u)

5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t) prepared by above Step 1 was added to the catalyst solution containing Grubb's (I) catalysis such as ruthenium dissolved in organic solvent such as CH_2Cl_2 to give 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19(d, J=8.4Hz, 2H), 6.83(d, J=8.4Hz, 2H), 6.25 (t, J=4.2Hz, 1H), 4.54 (s, 2H), 3.77 (s, 3H), 3.65 (s, 3H), 3.25(t, J=6.9Hz, 2H) 2.33 (t, J=7.3Hz, 4H), 2.24 (q, J=4.5Hz, 2H), 1.80 (t, J=7.2Hz, 2H) 1.56(s, 2H)

Step 3. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1)



4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u) prepared by Step 2 dissolved in alcohol solvent was reacted with amine salt to give 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.15 (m,2H), 6.83 (d,*J*=7.8Hz, 2H), 6.28 (br t, 1H), 4.53 (s, 2H), 3.76 (s, 3H), 3.25(dt, *J*A=7.5Hz, *J*B=1.8Hz, 2H), 2.38-2.23 (m, 6H), 1.85-1.76 (m, 2H)

Example 96. Preparation of 4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide (v2)

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide (v2) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

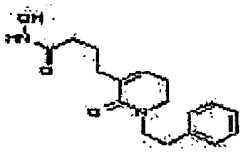
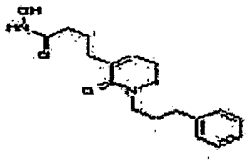
Example 97. Preparation of N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v3)

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v3) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

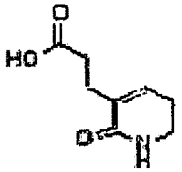
Example 98. Preparation of N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v4)

N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v4) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

[Table 20]

Example	Chemical structure	NMR spectrum data
96		7.29-7.13(m,5H),6.24(br t,1H), 3.56 (t,J=7.56Hz 2H), 3.31-3.29 (m, 1H), 3.16 (t, J=6.9Hz, 2H), 2.80(t, J=7.2Hz, 2H), 2.14-2.03 (m, 5H), 1.66-1.61 (m, 2H)
97		7.29-7.17(m,5H), 6.32(br t,1H), 3.46 (t,J=7.3Hz 2H), 3.35 (t, J=5.9Hz, 2H), 2.63 (t, J=7.6Hz, 2H), 2.37-2.28(m, 5H), 1.99-1.73 (m, 5H)
98		7.29-7.15(m,5H), 6.31(br t,1H), 3.45 (t,J=6.5Hz 2H), 3.32 (t, J=7.1Hz, 2H), 2.64 (t, J=7.0Hz, 2H), 2.27(d, J=7.2Hz, 6H), 1.60 (s, 6H)

Example 99. Preparation of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g)

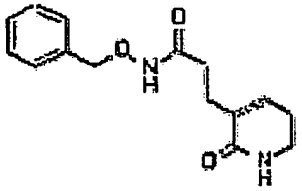


50mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (0.157 mM) was dissolved in 1 ml of trifluoroacetic acid solution. Then 0.074ml of triethyl silane (0.465 mmol) was added thereto and the mixture was heated for 20 min at 80°C. The solvent was removed *in vacuo* and the remaining residue was recrystalized with mixture solution of methanol and ethylacetate to give 13mg of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g) (yield : 50%).

^{1}H-NMR (300 MHz, CD_3OD), δ 6.51(m, 1H), 3.31(m, 2H), 2.50(m, 4H), 2.32(m, 2H)

^{13}C-NMR (75 MHz, CD_3OD), δ 176.7, 168.6, 138.4, 134.5, 40.3, 34.1, 27.1, 25.0

Example 100. Preparation of N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (h)



29mg of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g) was dissolved in 0.5 ml of DMF solution (0.171mM). 30mg of $BnONH_2 \cdot HCl$ (0.188 mM), 0.033ml of diisopropyl methylamine (0.189 mM), 43mg of EDC (0.224 mM) and 5mg of DMAP (0.041 mM) were added thereto and the mixture was stirred for overnight at room temperature. The mixture was diluted with 7 ml of ethyl acetate and washed with 5% HCl (1 ml) and 1ml of sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:20) solvent mixture as an eluant to give 126 mg of the title compound (h) (yield : 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.28(s, br, 1H), 7.35(m, 5H), 6.45(s, br, 1H), 5.70(s, br, 1H), 4.87(s, 2H), 3.47(s, br, 2H), 2.53(m, 2H), 2.27(m, 4H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1, 166.9, 137.8, 135.6, 133.0, 129.1, 128.5, 78.0, 39.7, 32.8, 26.9, 24.1

Example 101. Preparation of 3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)

Step 1. Preparation of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (f)

310mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d) (0.93 mM) was dissolved in 3 ml of trifluoroacetic acid solution. Then 0.222ml of triethyl silane (1.395 mmol) was added thereto and the mixture was heated for 20 min at 80°C. The solvent was removed *in vacuo* and the remaining residue was diluted in 20ml of chloroform. The organic layer was washed with 5ml of sat. $NaHCO_3$ solution and 5ml of sat. NaCl solution. Then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc solvent as an eluant to give 126mg of the title compound (f) (yield : 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ6.64(s, br, 1H), 6.35(t, *J*=3.0 Hz, 1H), 3.59(s, 3H), 3.31(m, 2H), 2.48(m, 4H), 2.26(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ173.4, 166.8, 136.1, 133.5, 51.4, 39.5, 33.1, 26.0, 24.0

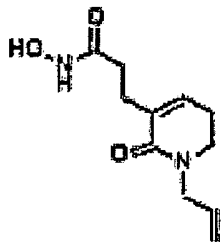
Step 2. Preparation of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i1)

0,220ml of NaHMDS solution (1.0 M in THF, 0.22 mM) was added to 0.5ml of the THF solution containing 40mg of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (0.218 mM) prepared by the Step 1 in a dropwise manner at -79 °C and stirred at -79 °C for 30 mins. After 0.028ml of allyl bromide (0.327 mM) was added to the reaction mixture, the mixture was stirred at 0 °C for 3 hrs. The reaction mixture was quenched by 2ml of sat. NH_4Cl solution and then the organic layer was extracted with 7ml of ethyl acetate. The combined organic layer was washed with 2ml of sat. NH_4Cl solution and 2ml of sat. NaCl solution. Then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc/hexane (1:2) solvent mixture as an eluant to give 36mg of the title compound (i1) (yield : 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.28(m, 1H), 5.74(m, 1H), 5.14(m, 2H), 3.99(d, *J*=5.7 Hz 2H), 3.61(s, 3H), 3.27(t, *J*=6.9 Hz, 2H), 2.51(m, 4H), 2.27(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.6, 164.6, 134.3, 134.1, 133.3, 117.1, 51.4, 49.0, 44.6, 33.3, 26.6, 23.8

Step 3. Preparation of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)



24mg of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i1) prepared from the above Step 2 was dissolved in methanol solution (0.11 mM) and then 0.122ml of 1.7M NH_2OK suspension solution (0.207 mM) was added thereto

at 0°C and stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate solution, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:10) solvent mixture as an eluant to give 11 mg of the title compound (j1) (yield : 48%).

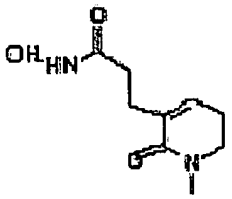
^{1}H-NMR (300 MHz, $CDCl_3$) : δ6.39(br t, 1H), 5.78-5.67(m, 1H), 5.17(d, *J*=5.4 Hz, 1H), 5.12(s, 1H), 3.98(d, *J*=5.4 Hz, 2H), 3.30(t, *J*=7.0 Hz, 2H), 2.54-2.28 (m, 6H)

Example 102. Preparation of N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (j2)

Step 1. Preparation of 3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i2)

0.22ml of 1.0M NaHMDS solution in THF (0.22 mM) was added to 0.5ml of THF solution containing 80mg 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (f) prepared from the step 1 in Example 3 (0.44 mM) in a dropwise manner at -79 °C and then stirred for 30 min. After 0.48ml of methyl bromide (0.48 mM) was added to the reaction mixture, the solution was stirred at 0 °C for 3 hrs. The reaction mixture was quenched by 2ml of sat. NH_4Cl solution and then the organic layer was extracted with ethyl acetate (7 ml). The combined organic layer was washed with 2ml of sat. NH_4Cl solution (2 ml) and 2ml of sat. NaCl solution subsequently. Then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc solvent as an eluant to give 62mg of the title compound (i2) (yield : 72%).

Step 2. Preparation of N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (j2)



50mg of 3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester prepared from the above Step 1 was dissolved in methanol (0.25 mM)

and then 0.122ml of 1.7M NH_2OK suspension solution in methanol (0.207 mM) was added thereto at 0°C and the resulting mixture was stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:20) solvent mixture as an eluant to give 19 mg of the title compound (j2) (yield : 35%).

^{1}H-NMR (300 MHz, CD_3OD) δ 6.15(t, J=4.3 Hz, 1H), 3.41(t, J=7.2 Hz, 2H), 2.97(s, 3H), 2.51(t, J=7.5 Hz, 2H), 2.35(m, 2H), 2.22(t, J=7.5 Hz, 2H)

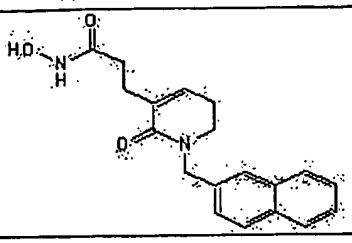
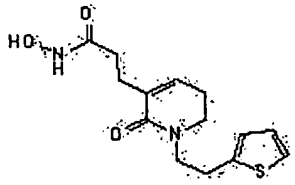
Example 103. Preparation of N-hydroxy-3-(1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide

70mg of 3-[1-(Naphthyl-2-yl)methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in methanol solution (0.22 mM) and then 0.64ml of 1.7M NH_2OK suspension in methanol (1.08 mM) was added thereto at 0°C and the resulting mixture was stirred for 5 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid and concentrated *in vacuo*. The resulting solid was filtered with 10% methanol/chloroform solvent mixture and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:9) solvent mixture as an eluant to give 61 mg of the title compound (*See* Table 21) (yield : 95%).

Example 104. Preparation of N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide

60mg of 3-[2-oxo-1-(2-thiophen-2-yl)ethyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in methanol to be 0.20 mM solution and then 0.6ml of 1.7M NH_2OK suspension solution in methanol (1.02 mM) was added thereto at 0°C and the resulting mixture was stirred for 5 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid and concentrated *in vacuo*. The resulting solid was filtered with 10% methanol/chloroform solvent mixture and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:9) solvent mixture as an eluant to give 44 mg of the title compound (*See* Table 21) (yield : 73%).

[Table 21]

Example	Chemical structure	NMR spectrum data
103		8.07-7.99 (m, 1H), 7.83-7.74 (m, 2H), 7.50-7.29 (m, 4H), 6.32 (br t, 1H), 5.01 (s, 2H), 3.44(s, 2H), 3.15 (q, *J*=6.9 Hz, 2H), 2.71-2.54 (m,2H), 2.42 (s, 2H), 2.09 (s, 2H)
104		7.11 (d, *J*=4.8 Hz, 1H), 6.89 (t, *J*=3.9 Hz, 1H), 6.82 (s, 1H), 6.35 (br t, 1H), 3.64-3.59 (m, 2H), 3.22 (t, *J*=3.22 Hz, 2H), 3.09-3.04 (m, 2H), 2.54-2.50 (m, 2H), 2.35 (s, 2H), 2.20(s, 2H)

Example 105. Preparation of 3-(1-Benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-N-hydroxy-propionamide (e1)

Step 1. Preparation of Benzyl-pent-4-enyl-amine (b)

0.397ml of 5-Bromo-1-pentene (3.35 mmol) and 0.67 ml of diisopropyl ethylamine (3.96 mmol) were added to the reaction solution containing 0.74ml of benzylamine(a) (4.93 mmol) dissolved in acetonitrile with stirring and the mixture was stirred at room temperature for overnight. The reaction mixture was washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with EtOAc solvent as an eluant to give 236mg of the pure title compound (b) (yield: 44%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.24(m,5H), 5.92-5.78 (m,1H), 5.09-4.98 (m,2H), 3.80 (s, 2H), 2.67(t, *J*=7.5Hz,), 2.14 (q, *J*=7.5Hz,2H), 1.69-1.59 (m, 2H), 1.41 (br, 1H)

Step 2. Preparation of Preparation of 4-(Benzyl-pent-4-enyl-carbamoyl)-pent-4-enoic acid methyl ester (c)

320 mg of 2-methylene-pentane dionate-5-methyl ester (2.02 mmol), 340 mg of EDC (2.02 mmol) and 50mg of DMAP (0.405 mmol) were added to 0.5 M of reaction solution dissolving the compound (b) prepared by above step 1 in methylene chloride and the mixture was stirred for 5 hrs at room temperature. The resulting

mixture was diluted with ethyl acetate, and washed with 5% HCl solution (10 ml) and 10 ml of saturated $NaHCO_3$ solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 150mg of 4-[but-3-enyl-(2,4-dimethoxybenzyl)-carbamoyl]-pent-4-enoic acid methyl ester (c) (yield : 35%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31-7.14 (m,5H), 5.81-5.64 (m,1H) 5.12 (s,1H), 5.04-4.97 (m,3H), 3.65 (s ,2H), 3.56-3.46 (m,3H), 3.42-3.36 (m,1H), 3.33-3.31(m,1H), 2.85(d,J=3Hz, 2H), 2.65-2.45 (m, 4H), 2.07-2.01(m, 2H), 1.69-1.59(m, 2H)

Step 3. 3-(1-Benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-propionic acid methyl ester (d)

150 mg of the compound (c) (0.476 mmol) prepared by the above Step 2 was added to the catalyst solution containing 40 mg of ruthenium (0.047 mmol) dissolved in CH_2Cl_2. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with methanol/chloroform (1:10) solvent mixture as an eluant to give 108 mg of the title compound (d) (yield : 79%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28-7.26 (m, 5H), 5.99-5.94 (m, 1H), 4.63(s,2H), 3.60 (S, 2H), 3.21(t, *J*=6Hz 2H), 2.65(t, *J*=7.2Hz,2H), 2.48(t, *J*=6.9Hz,2H), 2.08-2.01 (m, 2H), 1.67-1.57(m, 2H)

Step 4. Preparation of 3-(1-Benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-N-hydroxy-propionamide (e1)

108 mg of compound (d) prepared by the above Step 3 was dissolved in methanol solution (0.376 mmol) and then 1,7 M methanolic suspension solution containing NH_2OK (1.315 ml, 2.63 mmol) was added thereto at 0°C and the resulting mixture was stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate solution, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:10) solvent mixture as an eluant to give 46 mg of the title compound (e1) (yield: 43%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ7.28-7.24 (m,5H), 6.20-6.02 (m,2H), 4.65 (s,2H), 3.26(d,J=3Hz,2H), 2.66-2.52 (m, 4H), 2.08-2.05(m,2H), 1.65-1.64(m,2H)

Example 106. Preparation of N-Hydroxy-3-[2-oxo-1-(3-phenyl-ethyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (2e)

N-Hydroxy-3-[2-oxo-1-(4-phenylethyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (2e) was prepared by the similar procedure described in above Example 105 (*See* Table 22).

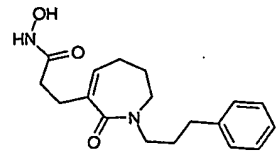
Example 107. Preparation of N-Hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (3e)

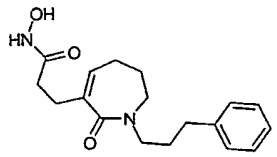
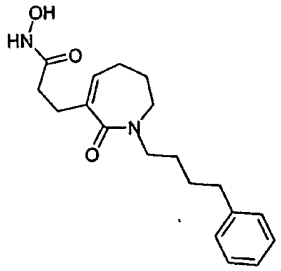
N-Hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (3e) was prepared by the similar procedure described in above Example 105 (*See* Table 22).

Example 108. Preparation of N-Hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (4e)

N-Hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (4e) was prepared by the similar procedure described in above Example 105 (*See* Table 22).

[Table 22]

Example	Chemical Structure	NMR Spectral data
106		7.3~7.20 (m,5H), 6.05 (t,J=6Hz,1H), 3.70 (t, J=6Hz, 2H), 3.17,(t,J=6Hz,2H), 2.89(t,J=6Hz,2H), 2.58-2.35(m,4H), 2.00 (t,J=6Hz,2H), 1.74(t,J=6Hz,2H)

107		7.31-7.12 (m, 5H), 6.11-6.05 (m,1H), 3.50 (br,2H) 3.25(br,2H), 2.76-2.47 (m, 6H), 2.17-2.09 (br,2H), 1.91-1.88 (br,2H)
108		7.27-7.13 (m,5H), 6.07-6.05 (m,1H), 3.44(br, 2H), 3.22(br, 2H), 2.62-2.43(m,6H), 2.09-2.07(br,2H), 1.84-1.82(br, 2H), 1.65-1.55(br,4H)

Experimental Example 1. Effect of the compound of the present invention on HDAC

To test the inhibiting effect of the compounds prepared from above Examples 1 to 108 on histone deacetylase (HDAC), HDAC Flurescent Activity Assay/Drug Discovery Kit (Biomol, USA) was used with nuclear extracts of HeLa cell as a HDAC source. Fluorogenic Histone Deacetylase Lysyl Substrate was used as substrate for HDAC and the test is based on the fact that the removal of acetyl group by HDAC activity causes the substrate to occur emmition wavelength in the ranging from 360 nm to 460 nm.

Various concentrations of the compounds of the present invention ranging from 0.01 to 10 μM were reacted with HDAC enzyme at 25°C for 20 minutes and equal volume of developer was added thereto. The fluorescence signal was detected at the wavelength in the range 350 to 460nm using by fluorescence spectrometer. IC_{50} value is defined as the concentration of the sample required to reduce the maximum fluorescence to a half and the result was shown in Table 2.

As shown in Table 2, it was confirmed that compounds of the present invention showed potent inhibiting effect on the activity of HDAC enzyme.

Experimental Example 2. Effect of the compound of the present invention on the tumor cell growth

PC-3 cells (ATCC, US), human prostatic carcinoma cell line, were cultured in RMPI 1640 supplemented with 10% fetal bovine serum.

Appropriate concentrations of cells ($5x10^4$ cells/ml) cultured in RMPI 1640 supplemented with 5% fetal bovine serum were poured into 96-well plate and incubated

at 37°C in 5% CO_2 condition. The day after the incubation, PC-3 cells were fixed on Time zero (T_0) plate by adding 50 μl/well of 50% trichloroacetic acid and the cell concentration was set to zero point by fixing the cells. In the cells treated with test samples, 50% TCA was added to each wells in 50ul/well after 48 hrs to fix the cells. The final concentration of adding test compounds were 0.01, 0.03, 0.1, 0.3, 1 μg/ml respectively. Then, each fixed plate was washed, dried and 100 μl/well of 0.4% reaction solution containing sulforhodamine B (SRB) reagent dissolved in 0.1% acetic acid was added thereto to stain the cells. 30 minutes later, the cell was washed with 0.1% acetic acid, dried at room temperature, and 10 mM of TRIS base (pH 10.5) was added thereto to dissolve the staining agent. Finally, the absorbance detected at 540 nm was measured and the value was conversed into percentage comparing with that of control group. IC_{50} ($\mu g/m\ell$), the concentration of the group required to inhibit the cancer cell growth by 50%, was calculated from the data (AA : IC_{50}'s < 1, A : IC_{50}'s < 5, B: IC_{50}'s < 10 and C : IC_{50}'s > 10). Also, the inhibiting activity of cell growth was expressed as various symbols in accordance with the potency of examples e.g., AA: closely equivalent (1~2 times), A: slightly weaker (3~5 times), B: weaker (5~10 times), C: very weaker (more than 10 times) than that of adriamycin used as a positive control group. The result was shown in Table 23.

As shown in Table 23, it was confirmed that compounds of the present invention inhibited HDAC directly and showed potent inhibiting effect on the activity of cancer cell growth, especially, PC-3 cancer cell.

[Table 23]

Example	HDAC inhibition	Cell growth inhibition	Example	HDAC inhibition	Cell growth inhibition
1	AA	A	31	A	A
2	AA		32	A	A
3	AA	AA	33	A	A
4	AAA	A	34		A
5	C		35		A
6	AA	B	36		A
7	AA	A	37		A
8	AA	A	38		A
9	C	A	39		A
10		AA	40		A
11		AA	41		B
12	AA	AA	42		AA
13	AA	A	43		A
14	A	B	44		B
15			45		B
16	C	C	46		B
17	C	C	47		
18		B	48		
19		B	49	AA	A
20	C	C	50	A	AA
21	C	C	51	A	C
22	C	C	52		
23	C	C	53		AA
24	C	C	54	C	A
25	C	C	55	AA	AA
26	C	C	56	AA	AAA
27	C	C	57	AA	AA
28		A	58	AA	B
29		A	59	AA	B
30		A	60	AA	B

Example	HDAC inhibition	Cell growth inhibition	Example	HDAC inhibition	Cell growth inhibition
61	AA	AA	85	C	
62	AA	AA	86	C	C
63	C	C	87	C	
64	C	C	88	C	
65	C	C	89	C	
66	C	C	90	C	
67	C	C	91	C	
68	C	C	92	C	C
69	C	C	93	C	
70	C		94	C	
71	C		95	C	C
72	C		96	C	
73	C	C	97	A	
74	AA	C	98	A	
75	AA	B	99	C	
76	A	C	100	C	
77	AA	A	101	C	C
78	C		102	C	C
79	C		103	C	B
80	C		104	C	B
81	A	C	105	C	C
82	C	C	106	C	C
83	C	C	107	C	C
84	C		108	C	C

Experimental Example 3. Toxicity test

Methods

The acute toxicity tests on ICR mice (mean body weight 25±5g) and Sprague-Dawley rats (235±10g, Jung-Ang Lab Animal Inc.) were performed using the

compounds of example 80. Four group consisting of 10 mice or rats was administrated orally with 4mg/kg, 40mg/kg, 400mg/kg and 4,000mg/kg of test sample or solvents (0.2 ㎖, i.p.) respectively and observed for 2 weeks.

Results

There were no treatment-related effects on mortality, clinical signs, body weight changes and gross findings in any group or either gender. These results suggested that the extract prepared in the present invention were potent and safe.

Hereinafter, the formulating methods and kinds of excipients will be described, but the present invention is not limited to them. The representative preparation examples were described as follows.

Preparation of powder

the compounds of example 80	50mg
Lactose	100mg
Talc	10mg

Powder preparation was prepared by mixing above components and filling sealed package.

Preparation of tablet

the compounds of example 80	50mg
Corn Starch	100mg
Lactose	100mg
Magnesium Stearate	2mg

Tablet preparation was prepared by mixing above components and entabletting.

Preparation of capsule

the compounds of example 80	50mg
Corn starch	100mg
Lactose	100mg
Magnesium Stearate	2mg

Tablet preparation was prepared by mixing above components and filling gelatin capsule by conventional gelatin preparation method.

Preparation of injection

the compounds of example 80	50mg

Distilled water for injection	optimum amount
PH controller	optimum amount

Injection preparation was prepared by dissolving active component, controlling pH to about 7.5 and then filling all the components in 2 ㎖ ample and sterilizing by conventional injection preparation method.

Preparation of liquid

the compounds of example 80	0.1~80g
Sugar	5~10g
Citric acid	0.05~0.3%
Caramel	0.005~0.02%
Vitamin C	0.1~1%
Distilled water	79~94%
CO_2 gas	0.5~0.82%

Liquid preparation was prepared by dissolving active component, filling all the components and sterilizing by conventional liquid preparation method.

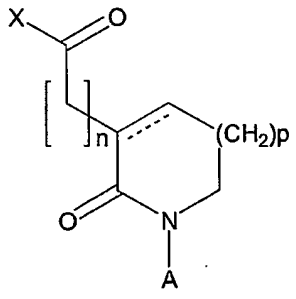
The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

INDUSTRIAL APPLICABILITY

As described in the present invention, the 2-oxo-cyclic compound of the present invention have potent anti-cancer activity, therefore, it can be used as the therapeutics for treating and preventing the cancer disease comprising lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer or cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter, or neoplasms of the central nervous system.

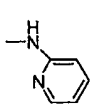
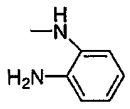
What is claimed is;

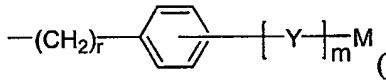
1. A use of a compound represented by the following general formula (I), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(I)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

A is an hydrogen, A1 group or  (A2),

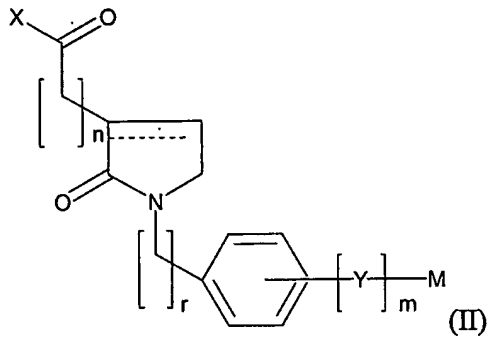
A1 is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group, wherein the Y in A2 substituted is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group, M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group, m and r is independently an integer of 1 to 5 respectively;

p is an integer of 0, 1 or 2;

n is an integer of 1 to 5;

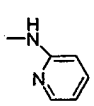
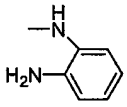
dotted line (⁼) means single bond or double bond.

2. A use of a compound represented by the following general formula (II), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(II)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

3. The use according to claim 2, wherein said compound is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-

propionamide,

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid,

N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide,

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide,

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide,

3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-

propionamide,

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

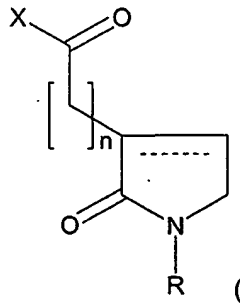
3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

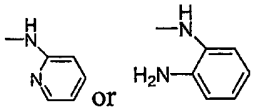
N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide.

4. A use of a compound represented by the following general formula (III), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(III)

wherein

X is a hydroxyl group, -NHOH, -$NHOCH_2Ph$,  or ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

5. The use according to claim 4, wherein said R is the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group.

6. The use according to claim 5, wherein said compound is one selected from the group consisting of;

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

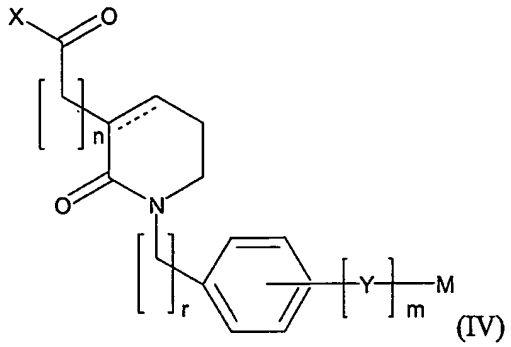
N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

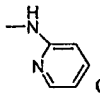
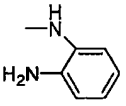
N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

7. A use of a compound represented by the following general formula (IV), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(IV)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (⎓) means single bond or double bond.

8. The use according to claim 7, wherein said compound is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetragydropyridine-3-yl]N-hydroxypropionamide,

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide,

N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide,

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid,

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide,

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid,

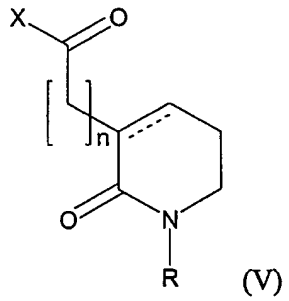
4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide,

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide,

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide,

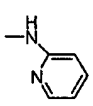
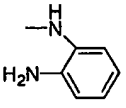
N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide.

9. A use of a compound represented by the following general formula (V), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(V)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (⎓) means single bond or double bond.

10. The use according to claim 9, wherein said compound is one selected from the group consisting of;

3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

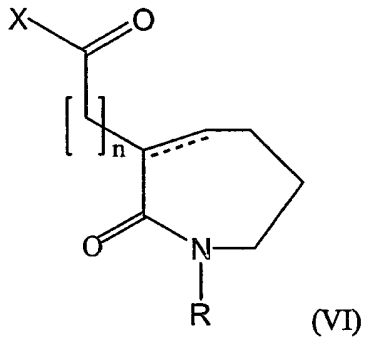
3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-hydroxy-3-(1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

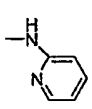
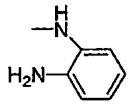
N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide.

11. A novel compound represented by the following general formula (VI), the pharmaceutically acceptable salt or the isomer thereof:



(VI)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is independently hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C4 carbon atoms substituted with a phenyl group which can be substituted with halogen atom or lower alkyl group;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

12. The compound according to claim 11, wherein said compound is one selected from the group consisting of;

N-3-(1-benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-ethyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-butyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide.

13. A use of the compound of general formula (VI) as set forth in claim 12 or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to treat or prevent cancer disease together with pharmaceutically acceptable carriers or diluents.

14. The use according to any one of claims 1 to 11 and 13, wherein said cancer disease comprises lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer or cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter, and neoplasms of the central nervous system.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/001764

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 31/4015

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 A61K 31/4015

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
STN(Caslink)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/24797 A1 (MERCK & CO.,INC.) 12 April 2001 See p73, compound 2-4a,b.	1 - 14
A	WO 02/078679 A2 (TOPOTARGET APS) 10 October 2002 See page 21 and claim1.	1 - 14
A	EP 1138680 A1 (PFIZER PRODUCTS INC.) 04 October 2001 See p40, Table 1.	1 - 14
A	WO 97/12902 (CHIROSCIENCE LIMITED) 10 April 1997 See the whole document.	1 - 14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 SEPTEMBER 2004 (07.09.2004)	07 SEPTEMBER 2004 (07.09.2004)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2004/001764

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